# NIH State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia in Adults

**June 13–15, 2005**

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**William H. Natcher Conference Center**
**National Institutes of Health**
**Bethesda, Maryland**

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National Institutes of Health

# Contents

# Introduction

## Background

Insomnia is the most common sleep complaint reported by women and men across all stages of adulthood, and for many, the problem is not episodic but chronic. Insomnia is both a symptom of certain conditions as well as a disorder with complex and, likely, multiple causes. Chronic insomnia is associated with a wide range of adverse effects, including depression; alcohol and drug abuse; difficulties with concentration and memory; and various cardiovascular, pulmonary, and gastrointestinal disorders. In addition to reduced quality of life and increased health care use reported by insomnia sufferers, the large number of people experiencing insomnia ultimately results in significant economic burden to society in lost productivity and health care costs.

Recent progress in the definition and diagnosis of chronic insomnia has been followed by the identification of a number of behavioral and pharmacological approaches that show promise for managing chronic insomnia symptoms. However, there has been limited guidance for clinicians in terms of choice of treatment for chronic insomnia. Available treatments include long-term use of hypnotic medications; off-label use of antidepressant, antipsychotic, or antihistamine medications; behavioral or nonpharmacologic interventions; or no treatment at all. In addition to potential benefits, each choice is associated with specific risks, and not all patients have access to behavioral interventions.

Research further defining the nature of chronic insomnia as well as a careful examination of strategies for symptom management is urgently needed to provide patients and their health care providers with options that will best control their symptoms and improve their quality of life.

## Conference Process

To address this need the National Institute of Mental Health and the Office of Medical Applications of Research of the National Institutes of Health (NIH) will sponsor a State-of-the-Science Conference on the Manifestations and Management of Chronic Insomnia in Adults on June 13–15, 2005, in Bethesda, MD. During the first 2 days of the conference, experts will present the latest scientific knowledge about chronic insomnia and available treatments. After weighing all of the scientific evidence, an independent panel will prepare and present a state-of-the-science statement answering the key conference questions:

- How is chronic insomnia defined, diagnosed, and classified, and what is known about its etiology?
- What are the prevalence, natural history, incidence, and risk factors for chronic insomnia?
- What are the consequences, morbidities, comorbidities, and public health burden associated with chronic insomnia?

- What treatments are used for the management of chronic insomnia, and what is the evidence regarding their safety, efficacy, and effectiveness?

- What are important future directions for insomnia-related research?

## General Information

On the final day of the conference, the panel chairperson will read the draft statement to the conference audience and invite comments and questions.

Conference sessions will be held in the Natcher Conference Center, NIH, Bethesda, Maryland.

The conference may be viewed live via Webcast at http://videocast.nih.gov/. Webcast sessions will also be available after the conference.

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, level B1, across the street from the main entrance to the Natcher Conference Center.

The telephone number for the message center at the Natcher Conference Center is 301–594–7302.

## Conference Sponsors

The primary sponsors of the conference are:

- National Institute of Mental Health, NIH
- Office of Medical Applications of Research, NIH

The cosponsors of the conference are:

- National Center for Complementary and Alternative Medicine, NIH
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- National Institute on Alcohol Abuse and Alcoholism, NIH
- Office of Research on Women's Health, NIH
- U.S. Food and Drug Administration

The Agency for Healthcare Research and Quality (AHRQ) provided additional support to the conference development.

## Financial Disclosure

Each speaker presenting at this conference has been asked to disclose any financial interests or other relationships pertaining to this subject area. Please refer to the material in your participant packet for details.

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

# AGENDA

**Monday, June 13, 2005**

8:30 a.m. Opening Remarks
**Richard K. Nakamura, Ph.D.**
Deputy Director
National Institute of Mental Health
National Institutes of Health

8:40 a.m. Charge to the Panel
**Susan Rossi, Ph.D., M.P.H.**
Deputy Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health

8:50 a.m. Conference Overview and Panel Activities
**Alan I. Leshner, Ph.D.**
Conference and Panel Chairperson
Chief Executive Officer
American Association for the Advancement of Science
Executive Publisher
*Science*

## I. How Is Chronic Insomnia Defined, Diagnosed, and Classified, and What Is Known About Its Etiology?

9:00 a.m. Definition, Diagnosis, Classification, and Etiology of Chronic Insomnia
**Daniel J. Buysse, M.D.**
Professor of Psychiatry
Western Psychiatric Institute and Clinic
University of Pittsburgh Medical Center

9:20 a.m. Insomnia in Children and Adolescents
**Judith Owens, M.D., M.P.H.**
Director
Pediatric Sleep Disorders Clinic
Associate Professor of Pediatrics
Brown Medical School
Division of Pediatric Ambulatory Medicine
Rhode Island Hospital

**Monday, June 13, 2005 (continued)**

## I. How Is Chronic Insomnia Defined, Diagnosed, and Classified, and What Is Known About Its Etiology? (continued)

9:40 a.m. Psychological Models of Chronic Insomnia
**Kenneth Lichstein, Ph.D.**
Professor and Chair
Department of Psychology
University of Alabama

10:00 a.m. Physiological Models of Chronic Insomnia
**Gary S. Richardson, M.D.**
Senior Research Scientist
Division of Sleep Research
Henry Ford Hospital

10:20 a.m. Neurobiology of Insomnia
**Clifford B. Saper, M.D., Ph.D.**
Professor and Chair
Department of Neurology
Harvard Medical School
Beth Israel Deaconess Medical Center

10:40 a.m. Discussion
*Participants with questions or comments for the speakers should proceed to the microphones and wait to be recognized by the panel chair. Please state your name and affiliation. Questions and comments not heard before the close of the discussion period may be submitted at the registration desk. Please be aware that all statements made at the microphone or submitted later are in the public domain.*

## II. What Are the Prevalence, Natural History, Incidence, and Risk Factors for Chronic Insomnia?

11:10 a.m. Prevalence of Chronic Insomnia Among Adults and Associated Factors
**Daniel Foley, M.S.**
Epidemiologist
Center for Mental Health Services
Substance Abuse and Mental Health Services Administration
U.S. Department of Health and Human Services

**Monday, June 13, 2005 (continued)**

## II. What Are the Prevalence, Natural History, Incidence, and Risk Factors for Chronic Insomnia? (continued)

11:30 a.m. Natural History of Chronic Insomnia
**Terry B. Young, Ph.D., M.S.**
Professor
Department of Population Health Sciences
University of Wisconsin–Madison

11:50 a.m. Discussion

12:20 p.m. Lunch
Panel Executive Session

## III. What Are the Consequences, Morbidities, Comorbidities, and Public Health Burden Associated With Chronic Insomnia?

1:20 p.m. Psychiatric and Psychological Comorbidities
**Ruth Benca, M.D., Ph.D.**
Professor
Department of Psychiatry
Psychiatric Institute and Clinics
University of Wisconsin Medical School

1:40 p.m. Systematic Review of the Prevalence, Incidence, Natural History, and Factors Associated With Chronic Insomnia in Adults
**Manisha Witmans, M.D., FRCPC, Dip. ABSM, F.A.A.P.**
Pediatric Respirologist and Sleep Medicine Specialist
Assistant Professor
University of Alberta
Medical Director
Pediatric Sleep Program and Pediatric Sleep Medicine
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University of Alberta Hospital

2:00 p.m. Burden of Chronic Insomnia on the Individual
**Michael H. Bonnet, Ph.D.**
Professor
Department of Neurology
Wright State University School of Medicine

**Monday, June 13, 2005 (continued)**

## IV. What Treatments Are Used for the Management of Chronic Insomnia, and What Is the Evidence Regarding Their Safety, Efficacy, and Effectiveness?

2:20 p.m. Burden of Chronic Insomnia on Society
**Meir Kryger, M.D.**
Director
Sleep Disorders Centre
St. Boniface Hospital Research Centre, Winnipeg

2:40 p.m. Discussion

3:10 p.m. The Assessment of Treatment Efficacy
**Thomas Roth, Ph.D.**
Chief
Division of Sleep Research
Henry Ford Hospital

3:30 p.m. Treatment Epidemiology
**Nalaka S. Gooneratne, M.D., M.S.C.E.**
Director
Sleep Disorders Clinic for Seniors
Division of Sleep Medicine
University of Pennsylvania Medical School

3:50 p.m. Overview of Behavioral and Psychological Treatments of Chronic Insomnia
**Jack Edinger, Ph.D.**
Clinical Professor
Department of Psychiatry and Behavioral Sciences
Duke University School of Medicine

4:10 p.m. Efficacy of Behavioral and Psychological Treatments of Chronic Insomnia
**Charles Morin, Ph.D.**
Professor
École de Psychologie
Université Laval, Québec

4:30 p.m. Discussion

5:30 p.m. Adjournment

**Tuesday, June 14, 2005**

**IV. What Treatments Are Used for the Management of Chronic Insomnia, and What Is the Evidence Regarding Their Safety, Efficacy, and Effectiveness? (continued)**

8:30 a.m. Efficacy of Benzodiazepine Receptor Agonists in the Treatment of Chronic Insomnia
**James K. Walsh, Ph.D.**
Executive Director and Senior Scientist
Sleep Medicine and Research Center
St. John's/St. Luke's Hospitals

8:50 a.m. Benzodiazepine Receptor Agonist Safety
**Timothy Roehrs, Ph.D.**
Director of Research
Division of Sleep Research
Henry Ford Hospital

9:10 a.m. Systematic Review of the Efficacy and Safety of Drug Treatments and Combination Treatments in the Management of Chronic Insomnia in Adults
**Manisha Witmans, M.D., FRCPC, Dip. ABSM, F.A.A.P.**
Pediatric Respirologist and Sleep Medicine Specialist
Assistant Professor
University of Alberta
Medical Director
Pediatric Sleep Program and Pediatric Sleep Medicine
Stollery Children's Hospital
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9:40 a.m. Systematic Review of the Efficacy and Safety of Nondrug and Sequential Treatments in the Management of Chronic Insomnia in Adults
**Manisha Witmans, M.D., FRCPC, Dip. ABSM, F.A.A.P.**
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**Tuesday, June 14, 2005 (continued)**

**IV. What Treatments Are Used for the Management of Chronic Insomnia, and What Is the Evidence Regarding Their Safety, Efficacy, and Effectiveness? (continued)**

10:10 a.m. Discussion

10:40 a.m. Use of Over-the-Counter Medicine, Complementary and Alternative Medicine, and Alcohol in the Treatment of Chronic Insomnia
**Sonia Ancoli-Israel, Ph.D.**
Professor
Department of Psychiatry
University of California, San Diego School of Medicine

11:00 a.m. Use of Off-Label Medications in the Treatment of Chronic Insomnia
**W. Vaughn McCall, M.D., M.S.**
Professor and Chair
Department of Psychiatry and Behavioral Medicine
Wake Forest University Health Services

11:20 a.m. Discussion

Noon Adjournment

**Wednesday, June 15, 2005**

9:00 a.m. Presentation of the draft State-of-the-Science Statement

9:30 a.m. Public Discussion
*The panel chair will call for questions and comments from the audience on the draft state-of-the-science statement, beginning with the introduction and continuing through each subsequent section in turn. Please confine your comments to the section under discussion. The chair will use discretion in proceeding to subsequent sections so that comments on the entire statement may be heard during the time allotted. Comments cannot be accepted after 11:30 a.m.*

11:00 a.m. Panel Meets in Executive Session
*Panel meets in executive session to review public comments. Conference participants are welcome to return to the main auditorium to attend the press conference at 2:00 p.m.; however, only members of the media are permitted to ask questions during the press conference.*

2:00 p.m. Press Conference

3:00 p.m. Adjournment

*The panel's draft statement will be posted to www.consensus.nih.gov as soon as possible after the close of the conference and the final statement will be posted 4–6 weeks later.*

# Panel Members

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# Abstracts

The following are the abstracts of the proposed speaker presentations at the NIH State-of-the-Science Conference on Manifestations and Management of Chronic Insomnia in Adults. They are designed for use by the panelists and the participants in the conference, and as a reference document for anyone interested in conference deliberations. We are grateful to the authors, who summarized their materials and made them available in a timely fashion.

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# Definition, Diagnosis, Classification, and Etiology of Chronic Insomnia

**Daniel J. Buysse, M.D.**

## Definitions

The term "insomnia" can refer to either a symptom or a syndrome. The *symptom of insomnia* refers to a complaint of difficulty falling asleep; frequent or prolonged awakenings; or nonrestorative, poor quality sleep in an individual who has adequate opportunity and circumstances for sleep. Insomnia is not defined by sleep laboratory measures or any specific sleep duration. Because insomnia occurs only when there is adequate opportunity for sleep, it must be distinguished from sleep deprivation, in which the individual's short sleep duration results from inadequate opportunity. The *syndrome of insomnia*, or insomnia disorder, refers to the presence of insomnia symptoms together with significant distress or impairment of daytime function. The most common daytime impairments associated with insomnia include complaints of fatigue, mood disturbance, and impaired cognitive function. Actual daytime sleepiness is less common among individuals with insomnia. Table 1 presents recently developed research diagnostic criteria for the insomnia syndrome.[1] The term "insomnia" is often used imprecisely in both the medical literature and lay press. It should not be used to refer to sleep symptoms or complaints in a general sense, and it must always be distinguished from sleep deprivation, which has different causes and consequences.

**Table 1.** Research Diagnostic Criteria for Insomnia Disorder[1]

A. The individual reports one or more of the following sleep related complaints:
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep.
   3. Waking up too early.
   4. Sleep is chronically nonrestorative or poor in quality.

B. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.

C. At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the individual:
   1. Fatigue/malaise
   2. Attention, concentration, or memory impairment
   3. Social/vocational dysfunction or poor school performance
   4. Mood disturbance/irritability
   5. Daytime sleepiness
   6. Motivation/energy/initiative reduction
   7. Proneness for errors/accidents at work or while driving
   8. Tension headaches and/or gastrointestinal symptoms in response to sleep loss
   9. Concerns or worries about sleep

## Diagnosis

The diagnosis of chronic insomnia rests on a detailed clinical history. In particular, the history should focus on premorbid sleep characteristics, specific sleep symptoms, chronology of the problem, exacerbating and alleviating factors, and response to previous treatments. The insomnia problem should be viewed from a 24-hour perspective covering the patient's usual sleep and wake periods. This includes consideration of behaviors, cognitions, and environmental factors related to sleep and the sleep environment as well as the regularity of sleep hours from day to day. Other sleep-related symptoms must be assessed, including restless legs, snoring or breathing problems, and abnormal movements or behaviors during sleep. Daytime activities should be reviewed, with particular emphasis on exercise, regularity of work and daytime activities, limitations in these activities, daytime sleepiness, and napping. Finally, interviewing the patient's bed partner may elicit symptoms not evident to the patient.

A thorough medical and psychiatric history is also critical in the evaluation of insomnia, given the frequent occurrence of comorbid conditions. Medical conditions that cause breathing difficulty, pain, or limited mobility are especially important in evaluating insomnia complaints. Virtually any psychiatric disorder can also be associated with insomnia, including mood, anxiety, substance use, and psychotic disorders. A thorough medication and substance history is also essential and should include prescription and over-the-counter medications, substances such as caffeine and alcohol, and drugs of abuse.

Several other tools may aid the diagnostic process. Questionnaires may be useful to quantify sleep, psychiatric, and medical symptoms as well as a predisposition to worry or to have insomnia under stress. A 2-week *sleep-wake diary*, either in text or graphical form, allows patients to record their actual sleep hours and experiences and can help establish patterns of sleep and day-to-day variability. *Actigraphy* is an objective means of assessing rest-activity patterns, using a motion-sensitive device worn on the nondominant wrist. Similar to the sleep diary, actigraphy can be useful for examining temporal patterns, variability, and responses to treatment. *Polysomnography (PSG),* or a sleep study, is the gold standard for quantifying sleep and sleep disturbances. However, PSG is not routinely recommended for the evaluation of chronic insomnia[(2)] because, in most cases, PSG simply confirms the patient's subjective report without indicating a cause for awakenings. However, PSG may be useful in specific clinical situations, such as the suspicion of sleep apnea, periodic limb movements, or parasomnias.

## Classification

Classifications for insomnia are typically based on symptoms, duration, or presumed etiology. *Symptom-based classifications* (i.e., sleep onset, sleep maintenance, or mixed type insomnia) are of limited value, since the specific type of sleep complaint often varies within an individual over time,[(3)] and a majority of patients actually complain of more than one type of sleep disturbance. *Duration-based classifications,* such as transient (several days), short-term (up to 3 weeks), and long-term insomnia[(4)] or occasional, repeated brief and continued insomnia,[(5)] have had limited validation and are of questionable value given the high rate of chronicity and recurrence in insomnia. Transient and short-term insomnias are often related to specific psychosocial or environmental stresses, whereas chronic insomnia is more often related to intrinsic sleep disorders or primary insomnia.

*Etiology-based classifications* are the most useful for categorizing chronic insomnia. Specific classification systems include the International Classification of Disease (ICD)–9, the ICD–10,[6] the Diagnostic and Statistical Manual–Fourth Edition (DSM–IV),[7] and the International Classification of Sleep Disorders Second Edition (ICSD–2).[8] In general, the ICD has the broadest, least well-described categories; the DSM–IV has somewhat more specific categories; and the ICSD–2 has the most specific, with over 40 disorders that can present with insomnia symptoms. Each of the major classification systems describes three broad categories of etiologically-defined insomnia disorders.

## Etiology

The insomnia syndrome is commonly described as being *secondary* to other conditions, *associated* with other sleep disorders, or *primary* when no other etiology can be identified. *Secondary insomnia* refers to the insomnia syndrome when it is thought to be due to a medical or psychiatric disorder or to the effects or withdrawal from a substance/medication. This is the largest single group of chronic insomnia diagnoses seen in epidemiological studies and clinical samples.[9,10] In practice, however, it is often very difficult to distinguish whether insomnia is truly caused by these other conditions or whether it is simply comorbid.[11,12] *Insomnia associated with other sleep disorders* includes Restless Legs Syndrome, Obstructive or Central Sleep Apnea Syndrome, parasomnias, or other sleep disorders. *Primary insomnias* are those disorders in which insomnia is the major symptom, with no other disorder as a likely cause. The DSM–IV includes a single category for primary insomnia, whereas the ICSD–2 includes narrower categories of insomnia, such as psychophysiological, idiopathic, and paradoxical insomnias, which have received some support from validation studies.[13,14]

## Research Gaps and Needs

Despite its prevalence and widespread acceptance as a medical/psychiatric condition, major gaps and needs still exist in the definition and classification of chronic insomnia. These include: (1) a more precise determination of the cause of insomnia complaints—not all poor sleepers complain of insomnia, and not all insomnia patients have objectively poor sleep,[15] suggesting that sleep disturbance alone is not the sole cause; (2) a better understanding of the natural history of insomnia and its longitudinal association with medical and psychiatric conditions; (3) further validation of specific insomnia subtypes and differential treatment response; and (4) better tools for assessment and diagnosis, including consistent standards for diagnosis and reporting of results; validated assessment tools, including structured diagnostic interviews; and objective indicators of insomnia and its daytime impairments.

## References


1. Edinger JD, Bonnet MH, Bootzin RR, et al. Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. *Sleep.* 2004;27(8):1567–1596.

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# Insomnia in Children and Adolescents

## Judith Owens, M.D., M.P.H.

### Definition and Classification

Insomnia in children and adolescents, as in adults, is a symptom and not a diagnosis. The causes of childhood insomnia are varied, ranging from primarily medical (i.e., medication-related; associated with primary sleep disorders, such as obstructive sleep apnea) to the behavioral (i.e., related to poor sleep hygiene or inappropriate sleep-onset associations) and often represent a combination of these factors. While insomnia in adults is generally defined as difficulty initiating and/or maintaining sleep and/or early morning awakening and/or nonrestorative sleep in association with daytime consequences,[1] defining insomnia in children is much more challenging for a number of reasons. First, sleep problems in children must be viewed in the context of the normal, but nevertheless profound, physical, cognitive, neurobehavioral, and emotional developmental changes that occur throughout childhood. The range of childhood sleep behaviors that may be considered "normal" or "pathologic" is also wide, and these categorizations are often highly subjective. Unlike strict research definitions of sleep problems, the validity of parental concerns and opinions regarding their child's sleep patterns and behaviors must be considered in defining sleep disturbances in the clinical context. Parental recognition and reporting of sleep problems in children also vary across cultures[2] and age groups, with parents of younger children more likely to be aware of sleep concerns than those of school-aged children and adolescents.[3] Finally, any assessment of the impact of sleep problems in children must include an appreciation of the resulting stress on the family as well as an understanding of how daytime sequelae (i.e., mood, behavior, academic performance, etc.) in children frequently differs from those in adults.[4]

Keeping these caveats in mind, a recent American Academy of Sleep Medicine Task Force developed a consensus working definition of pediatric insomnia as follows:[5] Pediatric insomnia may be defined as difficulty initiating or maintaining sleep that is viewed as a problem by the child *or* caregiver, and the significance of the sleep problem may be characterized by its severity, chronicity, and frequency and associated impairment in daytime function in the child or family. It should be noted that, in most instances, the standard adult definition of insomnia may be applied to adolescents and that pediatric insomnia refers largely to children under the age of 12 years. In terms of specific diagnostic categories, the current International Classification of Sleep Disorders nosology[6] includes a number of insomnias that are common to both adults and children and several, outlined below, which are largely unique to the pediatric population:

**Sleep onset association disorder** is one of the most common sleep disorders in infants. In this disorder, a child learns to fall asleep only under certain conditions or associations, such as being rocked or fed and, thus, does not develop the ability to self-soothe. During the night, when a child experiences the type of brief arousal that normally occurs at the end of a sleep cycle (depending upon age, from 4–6 to 7–10 times a night) or awakens for other reasons, he or she is not able to get back to sleep without those same conditions being present. The infant then "signals" the parent by crying (or coming into the parents' bedroom if developmentally capable)

until the necessary associations are provided. Thus, the problem is generally one of prolonged night waking, rather than sleep onset delay, resulting in insufficient sleep.[7,8]

**Limit setting sleep disorder** is, in contrast, a disorder most common in children preschool-aged and older and is characterized by bedtime resistance and difficulty falling asleep, rather than night wakings.[9] Most commonly, this disorder is a result of a parent's inability or unwillingness to set consistent bedtime rules and enforce a regular bedtime, often exacerbated by the child's oppositional behavior. In some cases, however, the child's resistance at bedtime is due to an underlying problem in falling asleep caused by other factors (e.g., medical conditions or a primary sleep disorder) or a mismatch between the child's intrinsic circadian rhythm (delayed sleep-wake phase) and parental expectations.

**Food Allergy Insomnia** typically involves difficulty initiating and maintaining sleep related to gastrointestinal, dermatologic, etc. symptoms of atopy, usually in young infants. **Nocturnal Eating (Drinking) Syndrome** is a disorder occurring largely in infants that involves both "conditioned hunger" and sleep disruption related to consumption of large volumes of food/liquid during the night.

## Screening and Diagnosis

A number of studies have suggested that screening for sleep problems in pediatric practice is inadequate and may result in significant under-diagnosis of sleep disorders.[10,11] Several brief parent and self-report sleep survey tools have been developed to facilitate the screening process and yield important information about the nature and severity of any coexisting sleep complaints and possible daytime sequelae.[12–15] The clinical evaluation of a child presenting with a sleep problem involves a careful medical history to assess for potential medical causes of sleep disturbances; a developmental history and assessment of the child's current level of functioning (at school, home, etc.) in order to evaluate possible mood, behavioral, and neurocognitive sequelae of sleep problems; and a review of past and current sleep patterns (including usual sleep duration and sleep-wake schedule, often best assessed with a sleep diary) and sleep habits, such as bedtime routines, daily caffeine intake, and the sleeping environment, which may reveal environmental factors that contribute to the sleep problems.[16] Use of additional diagnostic tools, such as polysomnographic evaluation, is seldom warranted for routine evaluation of pediatric insomnia but may be appropriate if organic sleep disorders are suspected.[17]

## Etiology

Although sleep disturbances are transient in many children, there is considerable evidence that sleep problems may persist or recur in a substantial percentage.[18,19] A number of intrinsic and extrinsic variables may affect the type, relative prevalence, chronicity, and severity of sleep problems; these include child variables, such as temperament and behavioral style, individual variations in circadian preference, cognitive or language delays, and the presence of comorbid medical and psychiatric conditions; parental variables, such as parenting and discipline styles,[20] parents' education level and knowledge of child development, and mental health issues, such as maternal depression and family stress;[21] and environmental variables, such as the

physical environment (e.g., space, noise, perceived environmental threats to safety, room and bed sharing), family composition (e.g., number, ages, and health status of siblings and extended family members), and lifestyle issues (e.g., parental work status, competing priorities for time) as well as the cultural and family context within which sleep behaviors in children occur.

## Prevalence, Natural History, Incidence, and Risk Factors

It should be noted that, for the reasons cited above regarding the challenges in defining pediatric insomnia, prevalence and incidence rates are at best approximations; indeed, there are relatively little large-scale epidemiological data currently available to systematically define normal sleep and wakefulness patterns and sleep duration in infants, children, and adolescents.[22] It is estimated that approximately 25 percent of all children are reported to experience some type of sleep problem at some point during childhood.[23] Specific studies have reported an overall prevalence of a variety of parent-reported sleep problems[24] ranging from 25 to 50 percent in preschool-aged samples[9] to 37 percent in a community sample of 4- to 10-year-olds[3] to an upward of 40 percent in adolescents.[25] Furthermore, sleep concerns are one of the most frequent parental complaints in pediatric practices, following illness, feeding, behavior problems, and physical abnormalities.

Sleep disturbances in pediatric special needs populations and in children with comorbid psychiatric and medical conditions are extremely common. Significant sleep problems occur in 30–80 percent of children with severe mental retardation and in at least half of children with less severe cognitive impairment as well as in 50–70 percent of children with autism spectrum disorders.[26,27] Significant problems with initiation and maintenance of sleep, shortened sleep duration, irregular sleeping patterns, and early morning waking have been reported in a variety of different neurodevelopmental disorders, including Asperger's syndrome, Angelman's syndrome, Rett's syndrome, Smith-Magenis syndrome, and Tourette syndrome (increased nocturnal movements). Virtually all psychiatric disorders in children, especially mood and anxiety disorders, may be associated with sleep disruption.[28–30] Children with attention-deficit/ hyperactivity disorders are often reported by parents to have sleep-onset difficulties and restless sleep and present one of the more common chronic conditions for which sedatives are recommended by pediatric practitioners.[31–33] Sleep complaints are also common in children who have experienced severely traumatic events,[34] including physical and sexual abuse. A few recent studies have also begun to examine the role of sleep disturbances in a number of chronic medical conditions of childhood, such as asthma and atopy, burns, juvenile rheumatoid arthritis, and headaches, which may be particularly prone to sleep disruption.[35–38] Factors, such as the impact of hospitalization, family dynamics, underlying disease processes, and concurrent medications, are also clearly important to consider in assessing the bi-directional relationship of insomnia and chronic illness in children. Finally, vulnerable populations, such as children living with poverty, parental substance abuse and mental illness, or violence in the home, may be at higher risk for *developing* sleep problems as a result of such conditions as chaotic home environments and neglect; they may also be less likely to have sleep problems *diagnosed* because of limited access to health care services and may suffer more serious *consequences* from those sleep problems than their less vulnerable peers.

## Impact

In addition to their high prevalence and chronicity, recent evidence also suggests that sleep disorders may have significant short- and long-term consequences on children's academic and social functioning and health. A wealth of empirical evidence from several lines of research clearly indicates that children and adolescents experience significant daytime sleepiness as a result of inadequate or disturbed sleep and that significant neurobehavioral and performance impairments and mood dysfunction are associated with that daytime sleepiness.[39,40] Higher-level cognitive functions, such as cognitive flexibility and the ability to reason and think abstractly, appear to be particularly sensitive to the effects of disturbed or insufficient sleep.[4,41] Finally, health outcomes of inadequate sleep include an increase in accidental injuries (ranging from minor injuries to drowsy, driving-related motor vehicle fatalities)[42,43] and potential deleterious effects on the cardiovascular, immune, and various metabolic systems, including glucose metabolism and endocrine function.[44]

## Treatment

Any discussion of interventions in the treatment of pediatric insomnia must be prefaced by a statement regarding the importance of good sleep hygiene as a necessary component of every treatment package. Sleep hygiene refers to the basic environmental (e.g., temperature, noise level, ambient light), scheduling (e.g., regular sleep-wake schedule), sleep practice (e.g., bedtime routine), and physiologic (e.g., exercise, timing of meals, caffeine use) factors that promote optimal sleep. Furthermore, it should be emphasized that behavioral (i.e., nonpharmacologic) treatment approaches to insomnia in children have a well-documented empirical basis and are the mainstay of treatment, and that pharmacologic approaches should be largely considered adjuncts in the treatment of pediatric insomnia.[45,46] A brief description of the most common behavioral treatments for pediatric insomnia are included in Table 1.

There is a wide variety of medications that have been prescribed or recommended by pediatric practitioners for sleep disturbances in children, including antihistamines, chloral hydrate, barbiturates, phenothiazines, tricyclic antidepressants, benzodiazepines, alpha agonists, and melatonin.[47] The selection of medications in clinical practice which are prescribed for childhood sleep disturbances appears to be based largely on clinical experience, empirical data derived from adults, or small case series of medication use, as there are currently no medications approved for use as hypnotics in children by the U.S. Food and Drug Administration. Although the data are inadequate for an evidence-based approach to the use of pharmacologic agents for the treatment of pediatric insomnia, some basic clinical guidelines have recently been developed,[5] including, in almost all cases, medication is not the first treatment choice nor the sole treatment strategy; medication use, except for very self-limited circumstances, such as travel, should be viewed only within the context of a more comprehensive treatment plan; and medication should always be used in combination with nonpharmacologic strategies (e.g., behavioral interventions, parent education).

**Table 1.** Summary of Empirically-Based Nonpharmacologic Treatments for Pediatric Insomnia

| Intervention | Target Problems | Description | Selected References |
|---|---|---|---|
| Extinction | Bedtime disturbances/night wakings | Putting the child in bed and systematically ignoring inappropriate child behaviors (e.g., crying) until morning | (1) Rickert VI, Johnson CM. Reducing nocturnal awakenings and crying episodes in infants and young children. *Pediatrics.* 1988;81:203–212.<br>(2) Seymour FW, Bayfield G, Brock P, During M. Management of night waking in young children. *Aust J Fam Ther.* 1983;4:217–223. |
| Graduated extinction | Bedtime disturbances/night wakings | Combining extinction with scheduled parental checks | (1) Reid MJ, Walter AL, O'Leary SG. Treatment of young children's bedtime refusal and nighttime wakings: a comparison of "standard" and graduated ignoring procedures. *J Abnorm Child Psychol.* 1999;27:5–16.<br>(2) Hiscock H, Wade M. Randomized controlled trial of behavioural infant sleep intervention to improve infant sleep and maternal mood. *BMJ.* 2002;324:1062. |
| Early intervention/parent education | Bedtime disturbances/night wakings | Education of parents in the establishment of appropriate sleep habits (e.g., sleep routines, put to bed awake) to prevent the development of sleep problems | (1) Wolfson A, Lacks P, Futterman A. Effects of parent training on infant sleeping patterns, parents' stress, and perceived parental competence. *J Consult Clin Psychol.* 1992;60:41–48.<br>(2) Adair R, Zuckerman B, Bauchner H, Philipp B, Levenson S. Reducing night waking in infancy: a primary care intervention. *Pediatrics.* 1992;89:585–588.<br>(3) Kerr SM, Jowett SA, Smith LN. Preventing sleep problems in infants: a randomized controlled trial. *J Adv Nurs.* 1996;24:938–942. |
| Scheduled awakenings | Bedtime disturbances/night wakings/ parasomnias | Parent waking child 15–30 minutes before usual spontaneous awakening or parasomnia | (1) Rickert VI, Johnson CM. Reducing nocturnal awakenings and crying episodes in infants and young children: a comparison between scheduled awakenings and systematic ignoring. *Pediatrics.* 1988;81:203–212.<br>(2) Durand VM, Mindell JA. Behavioral intervention for childhood sleep terrors. *Behav Ther.* 1999;30:705–715.<br>(3) Frank NC, Spirito A, Stark L, Owens-Stively J. The use of scheduled awakenings to eliminate sleepwalking. *J Pediatr Psychol.* 1997;22:345–353. |
| Extinction with parental presence | Bedtime disturbances/night wakings | Parent feign sleep while staying in child's room and ignoring inappropriate child behaviors (e.g., extinction) | (1) Sadeh A. Assessment and intervention for infant night waking: parental reports and activity-based home monitoring. *J Cons Clin Psyc.* 1994;62:63–68. |

| Intervention | Target Problems | Description | Selected References |
|---|---|---|---|
| Positive bedtime routines | Bedtime disturbances | Parent developing a set bedtime routine that the child enjoys and associating these routines with positive behaviors (e.g., falling asleep quickly) | (1) Adams LA, Rickert VI. Reducing bedtime tantrums: comparison between positive routines and graduated extinction. *Pediatrics.* 1992;89:585–588. |
| Phase advance or delay chronotherapy | Delayed sleep phase syndrome | Systematically advancing or delaying child's sleep phase to desired sleep-wake schedule | (1) Okawa M, Uchiyama M, Ozaki S, Shibui K, Ichikawa H. Circadian rhythm sleep disorders in adolescents: clinical trials of combined treatments based on chronobiology. *Psychiatry Clin Neurosci.* 1998;52:483–490. |

Note: For an extended review see: (1) Mindell JA. Empirically supported treatments in pediatric psychology: bedtime refusal and night wakings in young children. *J Pediatr Psychol.* 1999;24:465–481. (2) Kuhn BR, Elliott AJ. Treatment efficacy in behavioral pediatric sleep medicine. *J Psychosomatic Res.* 2003;54:587–597.

In summary, the development of a common nosology, more detailed classification systems, and methodological tools designed to be both developmentally appropriate and culturally sensitive represent future goals in the field of pediatric insomnia. Research is needed to further delineate the extent and impact of pediatric insomnia in both the general population and special populations in order to understand the natural history of and risk factors for childhood insomnia and develop more effective and acceptable behavioral and pharmacologic treatment strategies.

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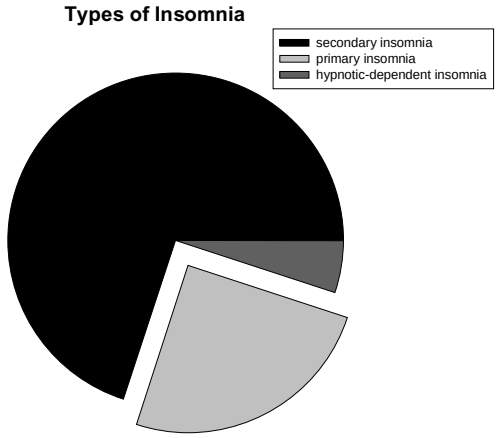
# Psychological Models of Chronic Insomnia

## Kenneth Lichstein, Ph.D.

A dozen hypotheses of psychological causes of primary insomnia have been advanced. This presentation will focus on the few that have gained broad acceptance: learning models, cognitive arousal, and personality traits. Primary insomnia, which assumes the absence of a disease/disorder/substance causal agent, represents about 25 percent of the insomnia population[(1)] (see Figure 1). Psychological factors are also contributory to both secondary insomnia and hypnotic dependent insomnia but are competing with other classes of factors, and it is difficult to parse the relative weight of causal factors in these types of insomnia.

**Figure 1.** Prevalence of Types of Insomnia




Note a methodological caution. Most research aspiring to demonstrate casual connections in this area have been lacking in methodological purity. Salient studies generally fall into one of the following categories: (1) uniform stimuli are presented to intact groups (insomnia present or absent) and differential responses are observed; (2) characteristics of intact groups (insomnia present or absent) are assessed and related to group membership; or (3) inferences are drawn about the cause of insomnia from the success of treatments targeting particular aspects of functioning. In these cases, classical requirements for the assertion of causal inference,[(2)] random assignment to groups, and controls for alternative explanations are not met.

## Learning Models

One of the first psychological treatments for insomnia was stimulus control,[(3)] and it remains one of the most effective. An operant rationale was originally presented wherein the bedroom signaled nonsleep behaviors (S stimulus value) due to habitual associations between that setting and sleep incompatible behaviors, such as reading, doing paperwork, watching television, and, more generally, wake time in the bedroom.

Classical conditioning has since been invoked, hypothesizing that conditioned aversion to the bedroom obstructs sleep.[4] In this model, transient insomnia introduced by intrusive events, as exemplified by bereavement or job stress, converts a neutral stimulus, the bedroom, into a conditioned stimulus evoking negative emotions. Such emotions promote deteriorating sleep that, in turn, escalates negative emotions, and this circular process sustains the conditioned stimulus properties of the bedroom.

There is indirect research to support learning models, such as the reverse first night effect in the laboratory occurring in people with insomnia. Credence is bolstered by the face validity of learning models and the success of stimulus control treatment, but there is little direct basic research validating this theory of insomnia.

## Cognitive Arousal

Falling asleep requires quiescent somatic and cognitive processes, and active thinking at bedtime is hypothesized to be mutually exclusive of sleep. Obstructive thoughts may be laden with sleep concerns or worry about matters unrelated to sleep, may focus on temporally distant or current content, and may assume a ruminative style. Comprehensive models of cognitive causation in insomnia also recognize maladaptive sleep expectations and selective attention to negative cues.[5]

There is more evidence to support the cognitive model than any other psychological cause of insomnia. By their own account, people with insomnia strongly endorse the cognitive model above all others,[6] they are more reactive to contrived threats at bedtime than normal sleepers,[7] and their presleep images and cognitions are more negatively toned than normal sleepers.[8,9] Among the few studies that used an analogue model and randomly assigned normal sleepers to conditions, poor sleep was more likely to emerge in those individuals exposed to contrived challenges.[10]

## Personality Traits

Trait personality theory could explain disturbed sleep,[11–13] and individuals with hypomanic/obsessive/anxious/depressed subclinical tendencies could be more vulnerable to irritants provoking somatic/cognitive arousal and resulting insomnia. Depending on the strength of the disposition, such individuals may experience either chronic or intermittent insomnia when their vulnerability is stirred by environmental pressure (a diathesis-stress model).

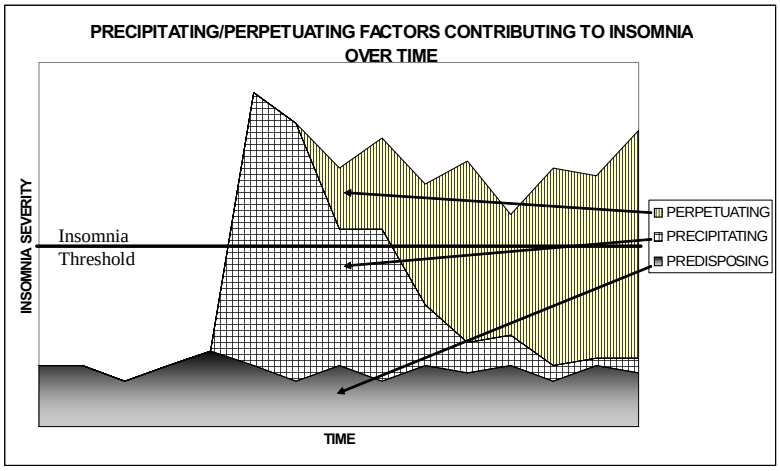
This view has been tested mainly by correlational studies that have attempted to measure the strength of association between assessed personality traits and insomnia presence. In general, these efforts have obtained weak to moderate results.

## Hybrid Model

Spielman[14] and his colleagues have advanced what has become known as the 3P model (see Figure 2), which incorporates aspects of all three models. Stable *predispositions* (e.g., anxiety proneness), varying *precipitants* (e.g., job stress), and varying *perpetuating* factors

(e.g., conditioned aversion to the bedroom) conspire to induce and maintain insomnia. Insomnia appears when the summative influence of these factors surpasses the individual's threshold coping level. As precipitants fade, perpetuating factors may swell, and the insomnia may survive long after the demise of the precipitants. Partial support for this heuristic comes from studies showing insomnia covaries with perceived stress,[15] but overall, this model remains unvalidated.

**Figure 2.** Spielman 3P Model




## Conclusion

Multiple psychological (and other) factors likely contribute to insomnia, the constellation of causal factors likely varies between individuals as well as within individuals over the insomnia course, and the weight of evidence supports a cognitive etiology.

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# Physiological Models of Chronic Insomnia

**Gary S. Richardson, M.D.**

## Introduction

Physiological models of insomnia are those that emphasize the role of physiological or neurophysiological factors in the pathogenesis of insomnia. A separate review (by Lichstein) considers models of insomnia that emphasize a psychological perspective. In addition, it should be noted that the focus for this review is on models for primary insomnia (insomnia without an identifiable medical, pharmacological, or psychiatric cause). The heterogeneity of underlying mechanisms in secondary insomnia limits the relevance of these models, and they will not be reviewed here. This review considers three broad categories of models for primary insomnia: sleep-wake dysregulation, circadian dysregulation, and hyperarousal.

## Sleep-Wake Dysregulation

Several models posit a deficiency in one or more pro-sleep factors as a cause of primary insomnia. For example, abnormalities in serotonin seen in depression are invoked as the mechanism of sleep disruption characteristic of that disorder.[1] Putative endogenous ligands of the benzodiazepine receptor have also been implicated.[2] Candidate compounds include neurosteroids with benzodiazepine-like activity at gamma-aminobutyric acid, type A (GABAA) receptors ("epalons").[3] Glucocorticoids inhibit neurosteroid synthesis,[4] providing a potential link between stress, hypothalamic pituitary adrenal activation, and reduced endogenous activity at benzodiazepine receptors.

Melatonin deficiency has also been proposed as a model for insomnia,[5] particularly in older patients in whom pineal production of melatonin is reduced.[6] While studies of the effects of melatonin "replacement" in older patients with reduced melatonin and insomnia support this model,[7] negative studies in unselected younger insomnia populations imply that this model does not generalize to the larger insomnia population.[8]

## Circadian Dysregulation

The importance of the circadian oscillator to normal sleep-wake expression[9] makes it an obvious potential candidate mechanism in insomnia. In patients with circadian rhythm sleep disorders, an abnormal phase relationship between the circadian oscillator and the sleep-wake rhythm results in secondary insomnia,[10] but it remains unclear whether more subtle alterations in circadian phase may contribute to sleep disturbance in primary insomnia. Phase abnormalities have been described in primary insomnia patients,[11] but it is unclear whether this is primary or secondary to the sleep complaint.

## Hyperarousal

An important feature that distinguishes patients with primary insomnia from those with secondary insomnia is "hyperarousal." The most direct manifestation of this is the prolongation of sleep latency during the day, despite disturbance of nocturnal sleep.[12] Assessments of other measures suggest that the prolongation of sleep latency is part of a broader physiologic arousal, an important component of which is the augmented activity of the sympathetic nervous system. Patients with chronic insomnia show elevated levels of circulating catecholamines,[13] increased basal metabolic rates,[14] increased body temperature,[15] and altered heart rate variability.[16] These data, coupled with the demonstration that induction of sustained physiological hyperarousal in normal sleepers with caffeine could mimic the signs and symptoms of primary insomnia,[17] led these authors to propose the "hyperarousal model" of primary insomnia.[18]

Perlis and colleagues distinguish between the physiological hyperarousal outlined above and the "cortical arousal" implied by studies showing increased high frequency activity in the electroencephalogram of primary insomniacs.[19] The cortical arousal model provides an explanation for the disproportionate subjective sleep disturbance characteristic of primary insomnia, proposing the heightened arousal at the wake-to-sleep transition impairs the amnesia that is a normal part of sleep onset.[20]

We have proposed a model, the corticotropin-releasing hormone (CRH) model of insomnia,[21] that builds directly on the previous hyperarousal models, extending them to include a specific central nervous system mechanism. The corticotrophin-releasing factor (CRF; also known as CRH) mediates important central aspects of the stress response, including activation of the sympathetic nervous system, hypothalamic pituitary adrenal axis, and central monoaminergic systems involved in alerting and cortical arousal.[22] The CRH is also central to stress-related sleep disruption in animals,[22,23] and the CRH dysregulation has been implicated in the pathogenesis of psychiatric disorders, such as depression.[24] An important feature of the CRH model of insomnia is that it suggests a mechanism for the demonstrated epidemiological link between primary insomnia and depression.[25]

## Conclusion

Physiological models provide an important foundation for future studies on the pathogenesis of primary insomnia. More recent models have sought to explain features of primary insomnia in addition to the nocturnal sleep disturbance.

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# Neurobiology of Insomnia

## Clifford B. Saper, M.D., Ph.D.

Over the last 10 years, much of the brain circuitry that regulates sleep and wakefulness has become more clear. In particular, wakefulness appears to be a product of the concerted action of an ascending arousal system, including monoaminergic and cholinergic neurons in the brainstem, peptidergic neurons (containing orexin or melanin-concentrating hormone) in the lateral hypothalamus, and neurons containing acetylcholine or gamma-aminobutyric acid (GABA) in the basal forebrain.[1] The major components of the ascending arousal system are inhibited by the ventrolateral preoptic nucleus (VLPO), which is made up of sleep-active, inhibitory neurons that contain both GABA and galanin. The VLPO neurons are, in turn, inhibited by the arousal systems, and their mutual inhibition results in the switching between wakefulness and sleep.[1,2]

The brain circuitry for insomnia, however, has not received much study. Georgina Cano, Ph.D., and I developed a rat model for insomnia in which rats are left to sleep in the cage of another male rat. They are quite territorial, and this causes considerable anxiety. The rats have difficulty falling asleep but eventually do sleep under homeostatic pressure; however, as that pressure wears off 4–6 hours into the sleep cycle, they begin waking up and cannot fall back asleep. When the brains of these rats were examined during this interval insomnia, it was found that there is an excess expression of Fos (a protein that is found in neurons that have recently been active) in the medial prefrontal cortex and central nucleus of the amygdala and the histaminergic tuberomammillary nucleus and noradrenergic locus coeruleus, while Fos activity in the VLPO is curtailed. It was also discovered that lesions of the medial prefrontal cortex and the amygdala have differential effects on the recovery of nonrapid eye movement versus rapid eye movement sleep and that drugs that affect the histaminergic system, likewise, differentially affect the two states. It is believed that drugs that act to reinforce the activity of the VLPO may be a better choice for reinstating sleep in stress-induced insomnia rather than using drugs (like classical GABA agonists) that work downstream of the VLPO and, thus, do not restore either slow-wave or rapid eye movement sleep adequately.[3]

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# Prevalence of Chronic Insomnia Among Adults and Associated Factors

## Daniel Foley, M.S.

Numerous epidemiological studies of sleep disturbances have shown that symptoms of insomnia, such as difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening, are common, especially among middle-aged and older adults. Comparative findings are hindered by differences in questions and criteria used to define prevalence as well as differences in study populations, including selection and participation bias. However, Dr. Ohayon's recent landmark review[1] of approximately 50 prevalence studies in various representative samples and cohorts of community-dwelling adults summarily reported roughly a 30–20–10 rule for prevalence rates. That is, approximately one-third of adults have symptoms of insomnia but only 15–20 percent report symptoms with daytime consequences and less than 10 percent are likely to meet the Diagnostic and Statistical Manual–Fourth Edition classification or other diagnostic criteria for chronic insomnia.[2]

In 1989, the National Institute of Mental Health's Epidemiologic Catchment Area study of sleep disturbances among nearly 8,000 adults aged 18 years and older showed that approximately 10 percent met diagnostic criteria for chronic insomnia and it was more common among women (12 percent) than men (8 percent).[3] Prevalence rates did not increase significantly with age or differ by race. Furthermore, among those without chronic insomnia at baseline, a similar proportion of men and women (6 percent) developed chronic insomnia approximately 1 year later. This incidence rate was also not associated with increasing age or race. However, the cumulative risk of chronic insomnia (i.e., the proportion of persons meeting criteria at baseline, follow-up, or both times) increased significantly from approximately 15 percent among those less than 65 years of age to approximately 19 percent among those 65 years of age and older, suggesting a greater persistence of symptoms in older adults. Other prevalence studies, especially of insomnia symptoms only (i.e., the 30-percent rule), consistently reported higher prevalence rates among women and generally showed complaints increased with age.[4–6] However, among persons aged 65 and older, the prevalence of chronic insomnia tends to remain stable across the older age groups at about 20–30 percent.[7] Yet, possible selection bias (i.e., noninstitutionalized adults), selective survival, and healthy participant effects associated with recruiting subjects over 80 years of age in cross-sectional epidemiological studies could have influenced such findings.[8]

Among the few longitudinal studies of chronic insomnia, results suggest that the higher prevalence of insomnia among women observed in cross-sectional studies may be due to a greater persistence of complaints over time among women rather than a higher incidence rate.[9–11] For example, in the National Institute on Aging's Established Populations for Epidemiologic Studies of the Elderly (EPESE), women with chronic insomnia at baseline were more likely than men to continue to have complaints in a 3-year follow-up (54 percent versus 48 percent), yet an equivalent proportion of men and women without symptoms at baseline had insomnia at follow-up (14 percent).[8]

In contrast, the EPESE biracial cohort study of sleep complaints showed that symptoms of insomnia were less prevalent among African Americans compared with Caucasians,[12] and 3-year follow-up data showed that African-American women had a significantly higher incidence of complaints (19 percent) compared with African-American men (12 percent) and Caucasians (14 percent).[11] Women of both races were more likely to persist with complaints at follow-up (58 percent) than men (36 percent).

Although a number of medical conditions are known to increase the risk of chronic insomnia, psychiatric disorders consistently show the strongest association with prevalence, incidence, and persistence of this disorder in epidemiological studies.[1] For example, in the Epidemiologic Catchment Area study, 40 percent of the insomniacs had a psychiatric disorder compared with 16 percent among those with no sleep complaints, and the incidence of major depression occurred in 10 percent of the insomniacs compared with less than 1 percent among those with no complaints.[3] In the EPESE study, about one-third of those with symptoms of chronic insomnia had depressed mood compared with roughly 10 percent among those without symptoms based on the Center for Epidemiologic Studies–Depression score of 16 or higher.[13] Furthermore, EPESE longitudinal data showed that among 4,000 older persons with neither depressed mood nor insomnia, only 28 percent of the new cases of insomnia (14 percent overall) concurrently developed depressed mood, as other associated factors included heart disease, stroke, hip-fracture, and respiratory problems as well as the use of sedatives and multiple over-the-counter medications.[9] In the absence of medical conditions and psychiatric disorders, the prevalence of chronic sleep complaints may be less than 3 percent.[14] Aside from the onset of medical conditions and psychiatric disorders, particularly in those under 65 years of age, chronic insomnia is also associated with alcohol and substance abuse,[1,3] smoking,[1,15] inactivity,[1,16] bodily pain from arthritis or other causes,[1,17] respiratory problems,[1,6,10] and work-related stress.[18]

In summary, chronic insomnia is pervasive among adults of all ages and there is a pressing need to better understand the nature and course of this epidemic condition. The limited epidemiological findings to date highlight the need for further longitudinal study of racial, ethnic, and other cultural factors, including marital status and lower socioeconomic status in addition to medical conditions and psychiatric disorders that affect the development and course of chronic insomnia in the population.[1,3,6,7,9] Consequently, a new generation of large, prospective cohort studies may be needed to facilitate an understanding of priorities for public health prevention and intervention strategies in this area.

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# Natural History of Chronic Insomnia

## Terry B. Young, Ph.D., M.S.

An understanding of the natural history of chronic insomnia, including the progression and remission of untreated incident insomnia, is critical to assessing the public health burden and developing feasible clinical strategies for this condition. Cross-sectional studies have established the high prevalence of insomnia in the general adult population as well as in patients in primary care and other clinical settings. However, longitudinal data that permit estimation of incidence and characterization of the course of chronic insomnia symptoms, free of selection biases and clinical intervention, are sparse.

### Methodological Problems in Documenting the Natural History of Chronic Insomnia

Incidence, progression, and remission for chronic conditions are ascertained by following a cohort of persons, initially free of the disorder, over time. With baseline and follow-up measurements, incidence is estimated by the proportion of those who were free of the condition at baseline that develop the condition within the study time interval. Because insomnia is characterized by a wide spectrum of duration, ranging from days to years, the follow-up period and number of measurement points must be considered in inferring natural history of chronic insomnia from prospective data. For example, a study assessing existing insomnia symptoms at baseline and 3 years later may report the 3-year remission of baseline insomnia, the stability or worsening over time, or the 3-year incidence of "new" insomnia. However, unless detailed questions are asked about symptom change, the actual dynamics of symptoms during the time period may not be captured. What may be identified as "chronic insomnia," (e.g., symptoms at both baseline and follow-up) may actually be two episodes of transient insomnia. Thus, caution is needed in inferring natural history from limited longitudinal data.

It is also important to recognize that the natural history and characteristics of insomnia in clinic and general populations are likely to differ. A high proportion of persons with insomnia do not seek care for their sleep problems, and thus, factors related to care seeking, including diverse factors, such as the ability to pay for medical care and comorbidity, may introduce biases that limit comparability of data or generalization.

### Estimates of Incidence, Remission, and Persistence of Insomnia Symptoms

In one of the earliest longitudinal studies of sleep problems in the general population, Ford and Kamerow[(1)] studied a multisite probability sample of adults. Individuals were classified as having insomnia if: (1) they reported ever having had a period of 2 weeks or more with trouble falling asleep, staying asleep, or waking too early; (2) had told a professional about it, took medication, or if it interfered with their life; and (3) the insomnia was not attributed to illness, alcohol, or drug abuse. The overall incidence of insomnia was 6.2 cases per 100 persons per year, with a slightly higher rate for women (6.8 percent) compared with men (5.4 percent) and an increase with age from 5.7 percent in persons 18–25 and 7.3 percent in those older than

65 years of age. The prevalence of persistent or chronic insomnia (i.e., positive response at baseline and 1-year follow-up) was relatively low but increased slightly with age, with 2 percent for ages 18–25 years and 4 percent for persons older than 65 years of age.

In a 1-year longitudinal study in Alemeda County, CA, of 2,380 adults who were 46 years and older, participants were asked about trouble falling or staying asleep nearly every day.[2] Although persons aged 80 years and older appeared to have higher point prevalences, there was no clear age trend. Persistent insomnia was considerably higher compared with that of the Ford et al. study—13 percent of the sample reported insomnia at both time points.

Breslau and colleagues, in a study of young adult enrollees of a Michigan health maintenance organization, also used an insomnia question in the style of the Diagnostic and Statistical Manual–Third Edition.[3] Data at baseline and follow-up indicated a 3.5 year incidence of 10.6 cases per 100 men and 14.8 cases per 100 women.

Questions regarding trouble initiating or maintaining sleep were included in a survey administered to a cohort of Swedish men in 1984 and 1994.[4] Based on responses from 2,602 men, the prevalence of severe or very severe (4 and 5 on a 5-point scale) problems with sleep onset or maintenance was 10 percent in 1984 and 11 percent in 1994. Change in prevalence over time was greatest for the younger age group, with a 4 percent increase in prevalence; change was minimal for those over age 50 years. Based on the number of cases given, the 10-year incidence was 8 percent, the prevalence of persistent insomnia was 4.5 percent, and the prevalence of remission was 5.7 percent (e.g., proportion of persons with insomnia in 1984 but not in 1994). Importantly, the authors noted that the baseline prevalence was considerably higher in those who died during the 10-year follow-up period compared with survivors (22.5 verses 11.1 percent) and that those who failed to respond to the follow-up survey similarly had a higher insomnia prevalence compared with responders. These findings stress the vulnerability of longitudinal data to incomplete follow-up.

Most previous studies have expressed insomnia in terms of having any symptom. However, in some areas of investigation, including tailoring therapy to specific symptoms, there is a focus on insomnia subtypes (e.g., onset, maintenance, and offset). Little is known about the stability of insomnia subtypes over time or whether the natural history of insomnia differs by subtype. In the single published study to date, Hohagen et al.[5] reported on the temporal stability of insomnia symptoms of difficulty initiating and maintaining sleep and undesired early morning awakening over a 4-month period in a sample of 2,512 primary care patients in Mannheim, Germany. Surprisingly, although 87 percent of patients with sleep complaints at baseline still had at least one symptom 4 months later; most reported different symptoms or combinations at follow-up. The investigators concluded that subdividing insomnia into subgroups (e.g., sleep onset, maintenance, early awakening) may not be a useful tool for diagnosis or research. Total remission (i.e., no symptoms at follow-up) of those with single symptoms at baseline ranged from 19 to 24 percent, those with two symptoms ranged from 10 to 18 percent, and those with three symptoms was 8 percent. One limitation of the study is that changes in hypnotic use occurred over the follow-up period and this may have affected symptom report. Three to 16 percent of the various symptom subgroups either started or stopped using hypnotics over the study period. Furthermore, the findings describe insomnia in a clinical sample and the natural history of insomnia among those seeking medical care may differ, due to comorbidity and many other reasons, from what is experienced in the general population.

The instability of distinct insomnia symptoms found in the clinical study of Hohagen and colleagues has also been found in a general population sample. Unpublished data on symptom changes over time from mailed surveys completed at baseline, 5-year, and 10-year follow-up were available from a sample of 3,900 middle-aged men and women participating in the Wisconsin Sleep Cohort Study. Participants were asked to rate the frequency of current difficulties with sleep onset, sleep maintenance, and too early awakening on a 5-point semiquantitative scale. While the overall point prevalence of the individual problems was fairly stable over time, there was considerable intrasubject change. Similar to the Hohagen study, of those reporting a particular symptom "often/almost always" at one time point, 50 percent or less reported similarly at the next time point. Five-year incidence, remission, and persistence is shown in the table below.

**Table 1.** Wisconsin Sleep Cohort: 5-Year Dynamics in Insomnia (Onset, Maintenance, or Offset Insomnia "Often or Always"), Wisconsin State Employees Ages 30–74 Years

| | **1987–1992 n = 3354** | **1992–1997 n = 2319** |
|---|---|---|
| Incidence, 5-year | 2.1% | 4.1% |
| Remission, 5-year | 1.9% | 1.6% |
| Persistence, 5-year | 24.1% | 24.3% |

While the prevalence of "chronic insomnia" was similar across both 5-year periods, 18.6 percent of the sample had insomnia based on data from both 5-year intervals. Interestingly, of those with 10-year chronic insomnia (defined as having at least one symptom "often or always" at baseline, 5-year, and 10-year follow-up) most (84 percent) had multiple symptoms. Onset, maintenance, and offset insomnias were simultaneously reported at all time points by 41 percent of this chronic insomnia group. The strongest predictor of 10-year chronic insomnia was the number of baseline symptoms. Participants with three symptoms had 4 times the odds of having insomnia 5 and 10 years later ($p < 0.05$). For women compared with men, the odds ratio for chronic insomnia was 1.3 ($p = 0.05$). Age, body mass index, education, exercise, and smoking were not significant predictors of chronic insomnia.

In summary, limited data suggest that chronic insomnia is manifested by middle age, with minimal incidence and remission, and is likely to be characterized by multiple symptoms.

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# Psychiatric and Psychological Comorbidities

**Ruth Benca, M.D., Ph.D.**

Insomnia is more frequently associated with psychiatric disorders than with any other medical illness.[1] Patients with symptomatic psychiatric disorders complain frequently of disturbed sleep, and insomnia symptoms are either part of the diagnostic criteria or associated clinical features of most psychiatric disorders. Polysomnographic studies have demonstrated sleep disturbance in virtually all categories of psychiatric illnesses, and patients with mood disorders tend to show the most robust and specific changes in sleep architecture, including loss of slow-wave sleep and abnormalities in rapid eye movement (REM) sleep (e.g., reduced REM sleep latency and increased proportion of REM sleep).[2] Not only is insomnia comorbid with psychiatric disorders, but also, symptoms of mood disturbance and irritability are recognized as associated features of insomnia.[3,4]

From an epidemiological standpoint, individuals with insomnia are significantly more likely to have a psychiatric disorder, particularly mood and anxiety disorders. In longitudinal studies, insomnia has been found to confer an elevated risk for future occurrence of mood disorders.[1] In patients with histories of mood disorders, insomnia is frequently the first symptom to appear in a recurrent episode of depression or mania[5–7] and often persists during periods of euthymia.[8]

The relationship between insomnia and psychiatric disorders is complex and poorly understood. Although insomnia may be worsened by psychiatric disorders and/or their treatments, it may not necessarily be the case that comorbid insomnia in a psychiatric patient is caused by the psychiatric disorder. Conversely, the fact that insomnia can predict the onset of depression suggests the possibility that some psychiatric disorders may be precipitated or exacerbated by sleep disturbance. The close association of insomnia with psychiatric disorders is likely related to common underlying mechanisms for sleep and mood regulation. Further research is needed to determine whether treatment of insomnia reduces its psychiatric and psychological comorbidities.

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# Systematic Review of the Prevalence, Incidence, Natural History, and Factors Associated With Chronic Insomnia in Adults

**Manisha Witmans, M.D., FRCPC, Dip. ABSM, F.A.A.P.**

Insomnia, or the inability to sleep, is the most commonly reported sleep problem in the industrialized world.[1] Estimates suggest that between 40 to 70 million Americans are affected by either intermittent or chronic sleep problems, representing approximately 20 percent of the population.[2] Although some risk factors and etiologies of insomnia have been identified, the nature of the relationships has not been fully elucidated. Some risk factors for insomnia that have emerged from data related to insomnia include female gender[3] and old age.[4] An association has also been found between insomnia and psychiatric and psychological disorders.[4] Insomnia has significant direct and indirect effects on the health and wellness of affected individuals. Individuals with insomnia are more likely to have hypertension (59 percent), nighttime heartburn (62 percent), and depression (74 percent).[3] The daytime consequences of chronic insomnia often include increased health care utilization, increased risk of depression, poor memory, reduced concentration, poor work performance, and perceived or real risk of failure at work.[5]

The Evidence-based Practice Center's objective was to conduct a systematic review of the prevalence, incidence, natural history, risk factors, and consequences of chronic insomnia in adults. A systematic search of 21 electronic databases was conducted. The following databases were searched: MEDLINE®, EMBASE, CINAHL®, Ovid MEDLINE® in-process and other nonindexed citations, Ovid OLDMEDLINE®, PsycINFO®, EBM Reviews–Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts, AMED (Allied and Complementary Medicine Database), HealthSTAR/Ovid HealthSTAR, EBM Reviews–Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Science Citation Index Expanded™, Biological Abstracts, Cochrane Complementary Medicine Field Registry, CAB Abstracts, SIGLE, OCLC Proceedings First, Dissertation Abstracts, Alt HealthWatch, NLM Gateway, and PubMed®.

A study was considered to be relevant to prevalence, incidence, and natural history of chronic insomnia if it met the following criteria: (1) the report was written in English; (2) participants were at least 15 years old; (3) it examined chronic insomnia defined as sleep disturbance of at least 1 month in duration; (4) it had a cross-sectional or cohort design; and (5) it assessed the prevalence, incidence, or natural history of chronic insomnia. A study was considered to be relevant to risk factors for chronic insomnia if it met criteria 1, 2, and 3 above; it had a cohort, case-control, or cross-sectional design; and it assessed one of the risk factors of interest. A study was considered to be relevant to consequences of chronic insomnia if it met criteria 1, 2, and 3 above; it had a cohort or cross-sectional design; and it assessed one of the consequences of interest. The studies were considered to examine chronic insomnia if this condition was defined as a sleep disturbance of 4 weeks or more, or the report explicitly mentioned that chronic sleep disturbance was examined. One of three instruments was used to assess the quality of studies, and data were analyzed qualitatively.

The interquartile range of prevalence of chronic insomnia varied from 8.5 to 24.3 percent across high quality studies of general populations to 19.8–53.7 percent across moderate quality studies of outpatient populations to 27.8–43.0 percent across moderate quality studies of clinical populations. Only one study provided data on the natural history of chronic insomnia; the remission rate was 13.1 percent after a 4-month follow-up. We found evidence to suggest that chronic insomnia is associated with older age; female gender; present or past psychiatric illness and psychological problems; medical conditions and poor general health; increased health care utilization; lower quality of life and social relationships; socioeconomic status (marital separation, unemployment, poorer working conditions, and lower social status); and decrements in memory, mood, and cognitive function. The relationship between chronic insomnia and race/ethnicity, shift-work, absenteeism, and work performance were not clear. The relationship between chronic insomnia and accidents or falls in the elderly and the direct and indirect costs of the disorder are also unclear.

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# Burden of Chronic Insomnia on the Individual

## Michael H. Bonnet, Ph.D.

The diagnosis of psychophysiological or primary insomnia has historically required a patient report of both poor sleep and "decreased functioning during wakefulness."[1] Requiring decreased daytime function may be related to the idea that insomnia produces reduced sleep at night and that this is similar to chronic partial sleep deprivation. Chronic partial sleep deprivation in normal individuals, whether by reduction in time in bed[2] or from production of the actual sleep stage distribution of insomnia patients in normals, [3] has been related to significant increases in objective sleepiness, significant decreases in psychomotor performance, and subjective fatigue. Types of decreased function that will be reviewed include decreased psychomotor performance, subjective dysphoria, decreased quality of life, and changes in physiological function.

At least 15 studies have examined various psychomotor performance tasks in patients with insomnia compared with controls (see review of studies prior to 2000[4]). Findings were placed into seven broad categories, including cognitive, vigilance, math, and reaction time tasks. An examination of significant test results within categories showed significant results at about chance levels with the possible exception of reduced ability to balance what was found in both studies in that area (effect size from one study was 3.1). As an example, effect sizes, where possible to calculate, averaged about 0.28 for cognitive performance measures.

Dysphoria is commonly reported by patients with insomnia. A number of studies have assessed various mood components in these patients. A review of studies prior to 2000[4] reported that 7 of 12 studies using the Stanford Sleepiness Scale found significantly greater sleepiness in patients compared to controls. Fatigue and other mood components, such as confusion, tension/anxiety, depression, and vigor, from the Profile of Mood States have also been significantly more negative in insomnia patients.[5,6] Across studies where calculation was possible, effect sizes for mood measures averaged 0.98.[6,7]

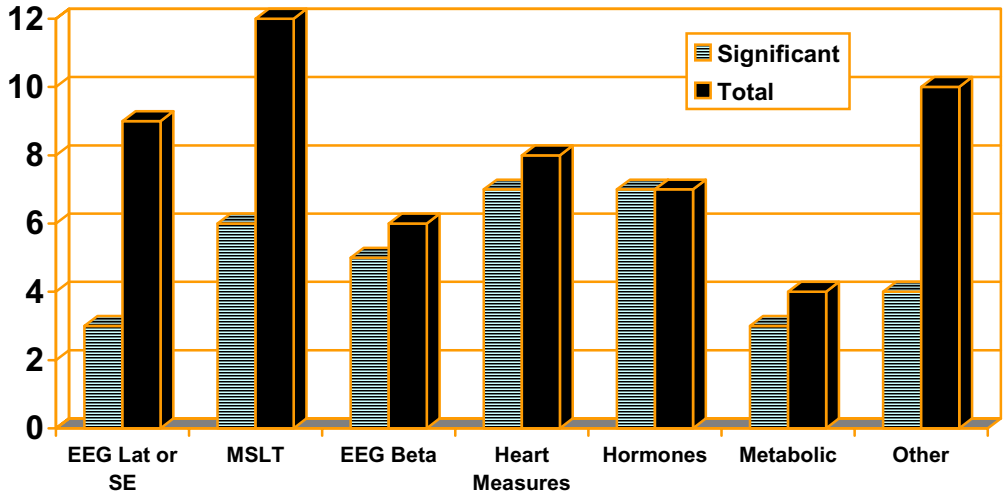
There are several means of assessing quality of life in patients. The Medical Outcomes Study Short Form SF–36 (SF–36) has been used to compare insomnia patients with depressed and congestive heart failure patients. Patients with severe insomnia had decreased quality of life that was greater than that in patients with congestive heart failure in pain, emotional effects, and mental health effects scales. Conversely, insomnia patients tended to report more physical problems than patients with depression.[8] These results are consistent with another study[9] that has shown that insomnia patients had more problems in all of the SF–36 scale areas compared with control subjects ($p < 0.0001$).

Quality of life may also be assessed by job performance. Self-reported poor sleepers in the Navy received significantly fewer promotions and were less likely to be recommended for reenlistment.[10] Subjectively identified insomnia patients report consequences at work, including significantly more errors, more accidents, and poor efficiency. Patients felt more fatigued and irritated with their children and had more health care consequences on a number of dimensions.[11] Effect sizes for patient subjective estimates of their performance decline

averaged 0.89.[7] Unfortunately, questionnaire studies cannot differentiate patients with primary insomnia from those with insomnia secondary to other factors, such as sleep apnea.

Several studies have found significantly increased physiological activation in patients with insomnia. At least 11 physiological measures have been shown to differ in insomnia patients compared with controls in more than 20 studies. The primary measures, along with the number of studies employing the test, significant results, and effect size estimates, can be seen in Figure 1.[5,12] At least 12 studies have examined the ability of insomnia patients to fall asleep during daytime nap opportunities (usually in the Multiple Sleep Latency Test) compared with matched controls (see Figure 1). These studies are of interest because, if patients suffer mainly from reduced sleep at night, their daytime nap latencies should be significantly reduced.[3] However, if patients primarily suffer from physiological hyperarousal as indicated from the physiological results above, their daytime nap latencies should be increased. Sleep latency was not significantly reduced in insomnia patients as compared to controls in any study. Sleep latency was significantly increased in insomnia patients as compared to controls in 6 of the 12 studies (and in 4 of 6 studies where electroencephalogram (EEG) criteria were used). The average sleep latency for the latter insomnia patients was 16.1 (+/- 4.4) minutes and for controls was 13.6 (+/- 4.8) minutes.[5] This difference was statistically significant ($t189 = 3.698$, $p < 0.001$), and the effect size was 0.55.

**Figure 1.** Significant Physiological Measures




Note: Lat = sleep latency; SE = sleep efficiency; MSLT = Multiple Sleep Latency Test.

Nine studies where insomnia patients were identified by subjective selection criteria and then had polysomnography allowed assessment of objective EEG measures of sleep latency and sleep efficiency. Only three studies reported either a significant increase in sleep latency or a significant decrease in sleep efficiency in insomnia patients compared to controls. The average EEG sleep latency and sleep efficiency averaged across studies were 22.5 versus 17.3 minutes and 81.8 versus 86.6 percent, respectively. Effect sizes were 0.24 and 0.49 for sleep latency and sleep efficiency.

## Conclusions

Primary insomnia patients frequently report dysphoric mood that is reflected by quality-of-life deficits that are at least as extreme as those reported by other patients with chronic illnesses. Despite complaints of poor performance, decreases in psychomotor performance, with the possible exception of balance, have not been reported above chance levels. This gap (reported versus objectively observed decrement) is similar to the degree of reported sleep disturbance, which is also greater than measured by objective EEG recordings. These findings and research modeling insomnia[3] suggest that the patient subjective complaints are not secondary to simple sleep deprivation.

The numerous physiological changes reported in patients with primary insomnia suggest an important physiological basis that is consistent with sympathetic nervous system activation and may be related to the increased risk for depression,[13] hypertension,[14] cardiac disorders,[15–17] or possibly mortality[17] in these patients over time. However, this implies that many current treatment studies (e.g., acute effects of therapy on EEG parameters or subjective sleep parameters) may not address the underlying disorder or ameliorate long-term risks. The data suggest: (1) increased attention to treatment of physiological activation in short-term studies followed by (2) controlled, long-term studies that confirm increased risk for depression and/or cardiovascular disease in placebo groups with decreased risk in treated groups. Such studies may provide necessary risk/benefit ratio information that could be used to justify or limit long-term pharmacological intervention in these patients.

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# Burden of Chronic Insomnia on Society

## Meir Kryger, M.D.

Epidemiological studies done all over the world suggest that symptoms of insomnia and the disorder (symptoms and daytime impairment) are very common. Because insomnia is so common it can therefore place a burden on society in at least several, sometimes overlapping, domains: direct treatment costs, indirect costs, workplace productivity, quality of life, and personal relationships.

### Insomnia Is Very Common

A very large number of studies from many countries using varying definitions have reported the epidemiology of insomnia. The range for the presence of symptoms was about 10–40 percent.[1,2] Although there are outliers, depending on the definitions used, a reasonable estimate of the prevalence of insomnia (symptoms plus daytime impact) is 5–15 percent. Thus, insomnia is common and the prevalence is in the same range as the most common medical conditions. Insomnia has an additional burden on society because of workplace accidents,[3] absenteeism,[4] work disability,[5] impaired quality of life,[6,7] and deterioration in personal relationships.[8] The degree in impairment of quality of life in patients with severe insomnia is in the same order of magnitude as in patients with congestive heart failure or depression.[7]

### Use of Health Care Resources

People with insomnia use health care resources (e.g., doctor visits and treatments) at a higher rate than people without insomnia. In most people, insomnia does not tend to remit; after 2 years, 59 percent of people with mild insomnia continue to have insomnia and 83 percent of people with severe insomnia continue to have insomnia.[9]

Hypnotics are widely used medications. In Scandinavian countries, the rate of hypnotic use is about 50 defined daily doses per 1,000 inhabitants per day.[1] This suggests that 5 percent of the population uses hypnotics on a daily basis. People with insomnia do not just use hypnotics. The population uses several sleep aids, including alcohol, over-the-counter products, and prescription medications. Only a minority of people with insomnia use medications. In one study involving approximately 7,000 patients in five health care maintenance organizations in the United States, 5.5 percent of people with insomnia symptoms only used hypnotics, while 11 percent used nonprescription medications.[10] In the group of patients with insomnia symptoms that had an adverse effect on daytime function, 11.6 percent used hypnotics while 21.4 percent used nonprescription medications. It has been estimated in the United States that in 2002 there were about 27 million prescriptions filled for hypnotics, worth about $1.2 billion. In the same year, a similar number of prescriptions were filled for nonhypnotics prescribed to treat insomnia; the most commonly prescribed was the antidepressant trazodone, accounting for approximately 10 million prescriptions.[11]

People with insomnia, whether associated with another comorbidity (medical or psychiatric) or not, are much more likely to see physicians than people without insomnia.[4,12] As a result of increased physician fees and drug costs, calculations based on medical claims (86,472 cases and 86,475 controls) have led to the estimation that the direct annual costs in the United States for elderly and nonelderly patients with insomnia were $5,580 and $4,220 higher than for matched controls.[13] Thus, at the very least, the presence of insomnia is a marker of an increase in health care costs. Estimates of total direct treatment costs in the United States vary between approximately $3 billion and $14 billion.[14,15]

## Indirect Costs

Indirect costs estimated from the same health plans calculated indirect costs related to absenteeism, use of short-term disability, and workers compensation. These indirect annual costs for elderly and nonelderly patients with insomnia were $5,580 and $4,220 higher than those for matched controls.[13] Estimates of indirect costs in the United States have been in the range of $80 billion.[14,16,17] It has been suggested that insomnia increases the risk of developing depression.[18] It is difficult to estimate the financial burden related to this.

## Conclusion

Although the data is imperfect, the weight of evidence suggests that insomnia does appear to place a significant impact on society as a whole. The true burden will not be known until consistent diagnostic criteria and definitions are used, there is accountability for the impact of the symptoms of insomnia in medical and psychiatric conditions, and the finding that insomnia may result in subsequent depression is factored in.

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# The Assessment of Treatment Efficacy

## Thomas Roth, Ph.D.

In defining the efficacy of hypnotics, it is important to distinguish between disturbed sleep and insomnia. Disturbed sleep refers to objective signs of sleep disruption, including excessive wakefulness before, during, and after the sleep period as well as the intrusion of arousals and awakenings into sleep per se. In contrast, insomnia is defined as a *symptom(s)* of difficulty falling or staying asleep or nonrefreshing sleep associated with some daytime consequence.[1] Evaluations of hypnotic efficacy have assessed aspects of both insomnia as well as disturbed sleep but have generally neglected the areas of daytime function and patient estimates of the adequacy of sleep. For example, in a study of patients reporting difficulty falling asleep, most efficacy trials will quantify the improvement in time to fall asleep but will not quantify the patient's perception of the adequacy of the posttreatment sleep initiation or the treatments' impact on aspects of daytime functioning.

There are three dimensions along which hypnotic efficacy can be defined. They are: (1) objective measures versus patient reports; (2) nocturnal sleep versus diurnal functioning; and (3) the nature of the patient population (primary versus comorbid insomnia).[2]

### Patient Reports Versus Objective Measures

A variety of instruments have been used to objectively quantify sleep.[3] At the current time, laboratory-based polysomnography (PSG) is recognized as the gold standard for the objective measurement of sleep. This is considered the standard, as it provides quantitative data on all important aspects of sleep physiology in a controlled environment. Increasingly, studies on insomnia are using home PSG. The advantage of home recordings is that they are a closer approximation of the actual clinical situation. The disadvantage is that there is the potential of data contamination by the home environment (e.g. noise, bed partner movements). On balance, home PSG may be more beneficial in studies of effectiveness whereas laboratory PSG may be more appropriate for efficacy trials. In further attempts to assay nonlaboratory sleep, a variety of other methods have been attempted. The most widely used non-PSG surrogate of sleep is the measurement of movement or actigraphy. Actigraphy has been used in a variety of sleep research contexts. Its utility seems to be greater in measuring sleep duration as opposed to sleep initiation, and it seems to be better in measuring sleep in normals as opposed to individuals with disturbed sleep or insomnia.

Finally, a grey area is the use of external observations of sleep. These represent neither objective measures of sleep nor patient reports. Examples in the literature include nurses' and caregivers' observations of sleep. These are not typically recommended in efficacy trials. In the area of patient reports, there are postsleep questionnaires in the sleep laboratory, typically used in conjunction with PSG recordings; sleep diaries, which are typically used at home over an extended period of time; and the patient's clinical global impression (PGI). The major advantage of sleep diaries is that they are typically done over an extended period of time and, hence, have the potential to provide information as to the consistency of sleep parameters across nights and the stable efficacy of the therapy.[4] While sleep diaries are used extensively, the analysis of

internight variability has rarely been a focus of inquiry. While the PGI is not routinely used, it is a potentially important parameter for assaying the patient's perception of improvement in insomnia symptomatology (nocturnal as well as diurnal) as an adjunct to the quantification of standard sleep parameters. When used, the PGI is typically done at the end of a trial or at several intervals during the trial (e.g., monthly).

## Nocturnal Sleep Versus Diurnal Endpoints

At the present time, primary measures, both in terms of PSG as well as patient reports, typically relate to sleep initiation, maintenance, and duration. Although there are multiple definitions of PSG-determined sleep onset, they are highly correlated. Patient estimates of improvement in sleep latency tend to correlate well with PSG measures.

Similarly, sleep duration is routinely defined by PSG or diary assays of total sleep time (TST). Less frequently, sleep efficiency is used as a measure of efficacy. Sleep efficiency is defined by TST and expressed as a percent of time in bed. The clear limitation of this endpoint is that you can improve sleep efficiency without positively impacting sleep by merely reducing time in bed. Reduction in time in bed (sleep restriction) has been shown to be an effective treatment for insomnia. However, that efficacy has to be defined using additional sleep endpoints. Sleep maintenance is a more complex endpoint than TST or sleep latency. One potential target, sleep maintenance, is often defined as wake time after sleep onset (WASO) and includes wake time during sleep as well as wake time after sleep before getting out of bed. WASO is a complex measure, as it incorporates the number and duration of awakenings. Thus, it is always advisable to evaluate both WASO and the number of awakenings to fully understand sleep maintenance. It has become apparent that some types of maintenance problems are associated with arousals rather than frank awakening. The evaluation of microarousals using a variety of physiological assays (e.g. electroencephalogram, electrocardiogram) will likely enhance our understanding of sleep maintenance and its treatment. More recently, individuals have begun evaluating middle of the night insomnia. Here, individuals have no difficulty falling asleep but awaken and have difficulty returning to sleep. Thus, efficacy can also be defined as the rapidity of sleep onset after an awakening. The final aspect of sleep that defines insomnia relates to its qualitative aspects. The terms "refreshing nature of sleep" or "quality of sleep" are often used in efficacy trials. In fact, in many clinical trials the "quality" of sleep is significantly improved. The question remains as to what is the physiological or functional correlate of this change. Individual studies have shown a correlation with ratings of sleep quality and either time in stage 3–4 nonrapid eye movement sleep or with TST. Others have speculated that sleep quality might relate to microarousals. In any case, the physiology and daytime consequence of the "quality of sleep" requires further research before we can understand its role in hypnotic efficacy. The daytime benefits associated with improvements in sleep-insomnia are the most neglected area in hypnotic efficacy trials. In part, this is due to the fact that insomnia morbidity research has, to date, failed to identify potential outcomes that might be improved with the successful treatment of insomnia. In the absence of clearly defined consequences associated with insomnia, investigators have focused on endpoints associated with sleep loss. Thus, patient reports of fatigue, alertness, and ability to function and concentrate have recently been shown to have some positive effects. Similarly, some studies evaluating quality of life have met with some mixed success. In contrast, objective measures of daytime function, such as memory, psychomotor and vigilance performance, and physiological measures of alertness (i.e., Multiple

Sleep Latency Test), have not met with much success.[5] The exception to this are isolated studies in transient insomnia and insomnia associated with pain. Clearly, this lack of consistent results suggests that insomnia morbidity is different than the consequences of sleep loss. Alternatively, it is possible that reversal of insomnia morbidity requires long-term treatment and most efficacy trials have been performed only for short periods of time (typically less than 4 weeks). Thus, long-term trials evaluating nonsleep-loss measures have the need to be performed. Measures which have been proposed include absenteeism, health care utilization, work productivity, accidents, and mood.

A final issue in understanding hypnotic efficacy relates to study populations. The vast majority of insomnia trials have been performed in patients with primary insomnia. In both population- and clinic-based studies, it is estimated that primary insomnia accounts for about 25–30 percent of the chronic insomnia population.[6] Clearly, studies are needed in insomnia comorbid with other conditions. Some areas which have been studied and show promise include insomnia associated with psychiatric disorders, pain conditions, and circadian rhythm disorders. In these studies, it is important to study not only sleep but also how improvements in sleep modify the course of the comorbid conditions.

Finally, geriatric and pediatric populations have been neglected populations. While pharmacokinetics studies are common in the elderly, long-term trials with age-specific endpoints (e.g. unintentional naps, memory function, balance) are scarce. By far, the most neglected area is pediatric insomnia. The indications for hypnotics as well as the benefits and risks are areas in desperate need of attention.

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# Treatment Epidemiology

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There have been significant advances in the therapeutic modalities used to treat insomnia over the past decade.[1,2] While numerous studies have examined the efficacy and safety of these agents, a smaller number of studies have examined the patterns of use for these treatments (see Table 1). These studies offer several insights into the epidemiology of insomnia treatments. First, self-treatment methods relying on over-the-counter (OTC) medications and alcohol are some of the most commonly cited insomnia treatments. The use of alcohol is particularly concerning because of the increased risk of alcohol abuse in insomniacs.[3] However, in general, 88 percent of individuals believe that alcohol is not beneficial for sleep.[4] Furthermore, while frequently mentioned, both OTC medications and alcohol are used on a less-consistent basis relative to prescription drugs. Roehrs et al. noted that 65–70 percent of patients using OTC medications/alcohol as a sleep aid used it for less than 1 week, while 62 percent of patients taking prescription drugs used them for more than 1 week.[5] OTC medications were used an average of 5.2 nights per month and alcohol an average of 6.8 nights per month. Second, there is very little data available regarding the use of behavioral/psychological treatments for insomnia, with the current data suggesting that they are largely underutilized. "Mental relaxation," for example, was recommended to chronic insomniacs by physicians only 6 percent of the time.[6] Nonprescription medication use has rarely been examined in detail as well, despite its high prevalence.[7] Third, the most commonly used prescription drugs for insomnia appear to be antidepressants and anxiolytics (U.S. Food and Drug Administration [FDA] off-label use).[8] Three of the five most commonly used drugs for insomnia drawn from a pharmaceutical database were antidepressants (trazodone [27.5 percent], amitriptyline [7.8 percent], and mirtazapine [6.7 percent]) and only two were FDA-approved drugs for insomnia (zolpidem [20.9 percent] and temazepam [5.6 percent]).[8]

Research examining trends in insomnia treatments has observed that the relatively low rate of prescription medication use has continued, with an overall decline of 24.4 percent from 1987 to 1996. Specifically, there has been a 53.7 percent decline in the use of FDA-approved insomnia drugs. In contrast, there has been a marked increase in the off-label use of antidepressants for insomnia during this same time period.[9] While these developments run counter to current treatment guidelines, several possible explanations have been proposed that are largely related to the regulatory environment in the United States.[8]

As noted earlier, the frequency of use and duration vary by treatment type. Prescription medications (e.g., hypnotics, anxiolytics, or antidepressants) were used for an average of 26 months, and within that time, the average number of consecutive nights of use was 35.[6] In Europe, nearly 30 percent of insomniacs using prescription hypnotics have used them for more than 4–5 years.[10,11] When comparing specific prescription medications, anxiolytics and antidepressants have even longer periods of use than hypnotics.[12]

**Table 1.** Selected Studies on the Epidemiology of Insomnia Treatment

| Study | Subjects (Response Rate)* | Characteristics/Year | Method | Findings |
|---|---|---|---|---|
| National Sleep Foundation, 2004 [14] | 1,473 (26%) | U.S., families with a child younger than 10 years old, 2003 | Random digit dial telephone calls | Rates of medication use in children (irrespective of sleep quality): 5% for those less than 3 years old and 3% for those 3 years of age or older. Types of medications used: 1–3% used OTC medications and 1% used prescription medications. |
| Roehrs et al., 2002 [5] | 1,325 (68%) | U.S. (Metropolitan Detroit area), ages 18–65, 2000 | Random digit dial telephone calls | In all subjects (insomniacs and noninsomniacs): 8% used prescription medications, 10% used OTC medications, and 10% used alcohol. Five percent used both prescription medications and alcohol. |
| Hatoum et al., 1998 [21] | 3,447 (46%) | U.S. (from five diverse managed care organization clinics), all ages, 1997 | Mailed survey | In those with insomnia: 5.5% used prescription medications for sleep (hypnotics and others) and 11.2% used OTC medications. In those with insomnia and daytime sleepiness: 11.6% used prescription medications and 21.4% used OTC medications. |
| Simon and VonKorff, 1997 [13] | 373 (61%) | U.S. (Puget Sound, WA, managed care primary care clinics), ages 18–65, 1996 | Face-to-face interview | In those with insomnia (“nearly every night”): 28% were on some type of psychotropic medication (14% used benzodiazepines and 19% used antidepressants). Most antidepressant use occurred in those with depression and insomnia: 38% of them were on antidepressants as compared to 13% of those with insomnia only. |

| Study | Subjects (Response Rate)* | Characteristics/Year | Method | Findings |
|---|---|---|---|---|
| Gallup Organization, 1995 [4] | 1,027 | U.S., population-based, ages 18 and older, 1995 | Random digit dial telephone calls with oversampling of insomniacs | In those with insomnia: 15% used a prescription sleep medication, 22–37% used OTC medications, and 16% used alcohol. Self-help techniques included: 64% reading, 50% warm bath, and 40% reduced caffeine and/or relaxation techniques. |
| Asplund, 1995 [19] | 6,143 (60.8%) | Sweden, ages less than 65, 1992 | Mailed survey | In all subjects: 13.5% of men and 22.3% of women used hypnotic medications. Usage rates increased with age (34.9% of women younger than 80). Twenty percent of hypnotic users used them every night. In insomniacs: 47.0% of men and 51.6% of women. |
| Ancoli-Israel and Roth, 1999 [6] | 1,000 (51%) | U.S., population based, ages 18 and older (15% were over 65), 1991 | Random digit dial telephone calls with oversampling of insomniacs. | Amongst occasional and chronic insomniacs: 21% used prescription medications, 23% used OTC medications, and 28% used alcohol. In chronic insomniacs only: more than 21% used prescription medications, 25% used physical exercise, 19% used reading, 17% used mental relaxation, and 11% used OTC medications. Thirty-nine percent had used some other kind of prescription sleeping medication (e.g., anxiolytics, etc.). |

*"Subjects" refers to the number of subjects who completed the survey/interview and on whom the study data is available.

Note: Percentages indicate subjects who have tried or used a given method for their insomnia at some point; OTC = over-the-counter.

Epidemiology studies have also examined the influence of demographic and comorbid factors on the use of insomnia treatments. Roehrs et al. noted that prescription drug users were more likely to be older than those using alcohol or OTC agents; alcohol users were mostly male, not married, and more likely to have rotating work schedules; and prescription medication users reported more severe insomnia, had higher scores on neuroticism scales, and were more likely to have lost days from work and social activities. There were no differences in racial, educational, or socioeconomic measures or in the nature of their insomnia.[5] Another study found that subjects with higher levels of chronic disease were more likely to use prescription drugs for their insomnia.[13] When comparing patient characteristics across different types of prescription drugs used to treat insomnia, gender and age were found to be significant: Females were more likely to receive antidepressants and less likely to receive hypnotics, while patients receiving hypnotics were older.[12]

A limited body of work has examined the epidemiology of insomnia treatments in special populations, such as children. The National Sleep Foundation's 2004 Sleep in America Survey focused on pediatric sleep and noted that parents who felt that their child had a sleep problem used medications 11 percent of the time.[14] Owens et al. surveyed primary care pediatricians regarding their management strategies for sleep disorders (not limited to insomnia) and observed the following: (1) medications were used with behavioral strategies in half of the cases; (2) 75 percent of pediatricians had recommended nonprescription medications; and (3) less than 50 percent had recommended a prescription medication. The mean duration of use for nonprescription medications was less than 1 week, while prescription drugs were more likely to be used for more than 1 month.[15]

Of all prescription and OTC drugs used to treat insomnia, 31 percent are consumed by patients aged 65–79, thus, making the elderly the most common users of insomnia medications.[16] In addition, the duration and frequency of use of insomnia treatments tends to be longer in the elderly.[7] While most studies of elders have found similar rates of use, one study of rural elders found lower rates of treatment with only 0.4 percent using OTC agents (primarily diphenhydramine) and 1.8 percent using prescription hypnotics (data on antidepressants/ anxiolytics was not obtained).[17] The elderly may also engage in counter-productive measures while attempting to self-treat their insomnia—59.1 percent watch television or listen to the radio to help themselves fall asleep.[18] To determine factors associated with treatment, Asplund conducted a study of 6,143 Swedish pensioners and noted that elders with poor health, cardiovascular disease, or chronic pain were more likely to use hypnotic drugs (odd ratio equals 1.6–2.3). There were no gender differences in the use of hypnotics.[19]

Another important observation highlighted by the treatment epidemiology data is that less than half of all chronic insomniacs have discussed their sleep disorder with their health care provider.[4,6] This has significant ramifications for interpreting the epidemiology of insomnia treatment. For example, of those patients who have spoken with a physician, only 1 percent discussed it with a sleep specialist, 8 percent with a psychiatrist, and the remainder spoke to their primary care doctor.[6] Many chronic insomniacs, especially the elderly, may tend not to discuss sleep problems with their health care providers because they view insomnia as a natural part of aging (34.8 percent) or are concerned they may be given a prescription sleeping pill by their physician (18.9 percent).[20] Lack of education is clearly a factor, with 72 percent of insomniacs stating that they did not understand the treatment options for insomnia.[4]

Several areas of significant research need can be identified from the preceding treatment epidemiology data:

1. Research on patient and physician factors that underlie the pervasive use of treatments that are not FDA-approved for insomnia, such as OTC agents, anxiolytics, and antidepressants—most of these agents have rarely, if at all, been rigorously studied as insomnia treatments, and the high prevalence of their use is concerning.

2. Examination of modifiable factors underlying the use of alcohol for insomnia with the ultimate goal of developing education/outreach programs to reduce inappropriate alcohol consumption for insomnia.

3. Investigation of the epidemiology of insomnia treatment in special populations (e.g., children, institutionalized and noninstitutionalized elders, ethnic and racial groups). For example, the largest consumers of insomnia medications are older adults, especially those with multiple comorbidities, but relatively little is known about what factors motivate their treatment decisions.

4. Research on the use of nonpharmacologic treatments (e.g., exercise, relaxation techniques) and nonprescription treatments. While there is evidence to suggest that as a category they are the most commonly used treatment modalities, there is very little information regarding the use of specific treatments, such as diphenhydramine (which may be overutilized), or cognitive-behavioral therapies (which, from our limited data, are significantly underutilized).

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# Overview of Behavioral and Psychological Treatments of Chronic Insomnia

## Jack Edinger, Ph.D.

For many insomnia sufferers, normal sleep-wake functioning becomes chronically disrupted through the development of poor sleep habits and conditioned emotional responses that either interfere with biological sleep-wake mechanisms or serve as inhibitors to sleep.[1] For example, daytime napping or spending extra time in bed in pursuit of elusive, unpredictable sleep may interfere with normal homeostatic sleep-controlling mechanisms and serve to reduce sleep drive on the ensuing night. Alternately, the habit of remaining in bed well beyond the normal rising time following a poor night's sleep may disrupt the circadian sleep-wake rhythm and make the subsequent night's sleep more difficult. The repeated association of the bed with unsuccessful sleep attempts, likewise, may result in a conditioned arousal in the home sleeping environment. Finally, failure to discontinue mentally demanding work and allot sufficient *wind-down time* before bed may make subsequent sleep initiation very difficult. Since any of these factors may contribute to and perpetuate sleep difficulty, behavioral/psychological interventions to correct these anomalies are often required to eradicate the chronic sleep difficulty.

Various *relaxation training* techniques, including progressive muscle relaxation training, autogenic training, imagery training, biofeedback, and hypnosis, have all been used to treat insomnia.[2,3] Regardless of the specific relaxation strategy employed, such treatment entails teaching the insomnia sufferer a formal exercise or set of exercises designed to reduce anxiety and arousal at bedtime so that sleep initiation is facilitated. Typically, multiple treatment sessions are required to teach relaxation skills that the patient is encouraged to practice at home in order to gain mastery of self-relaxation. The goal of all such treatments is that of assisting the insomnia sufferer in achieving sufficient relaxation skills so that insomnia resulting from sleep-related performance anxiety and bedtime arousal can be minimized.

*Stimulus control therapy,* an approach introduced by Bootzin,[4] is another treatment that has been used widely for insomnia management. This therapy is based on the assumption that both the timing (bedtime) and setting (bed/bedroom) associated with repeated unsuccessful sleep attempts over time become conditioned cues that perpetuate insomnia. In practice, stimulus control requires instructing the insomnia sufferer to: (1) go to bed only when sleepy; (2) establish a standard wake-up time; (3) get out of bed whenever awake for more than 15–20 minutes; (4) avoid reading, watching TV, eating, worrying, and other sleep-incompatible behaviors in the bed and bedroom; and (5) refrain from daytime napping. From a theoretical perspective, it is probable that strict adherence to this regimen not only corrects aberrant, sleep-disruptive conditioning, but it also likely reestablishes a normal sleep drive and sleep-wake rhythm.

*Sleep restriction therapy* entails limiting/restricting the time allotted for sleep each night so that the time spent in bed closely matches the individual's actual sleep requirement. The treatment, introduced by Spielman et al.,[5] grew out of the observation that many insomnia sufferers spend excessive time in bed each night in efforts to obtain their elusive sleep. Indeed, many such patients may experience excessive time awake each night simply because they are allotting far too much time for sleep. Typically, this treatment begins by having the patient

maintain a sleep log on which a record of each night's sleep is kept. After the patient has kept a sleep log for 2–3 weeks, the average total sleep time (ATST) is calculated from the information recorded. An initial time-in-bed prescription then may be set at the ATST or at a value only slightly higher than the ATST. Subsequently the time-in-bed prescription is adjusted up or down in small increments until a consolidated and restorative sleep pattern is established.

An alternate form of insomnia therapy, *paradoxical intention,*[6] relies on a form of *reverse psychology* to address sleep difficulties. Designed mainly to address sleep disruptive performance anxiety and exaggerated efforts to sleep, this treatment instructs the insomnia sufferer to remain awake as long as possible after retiring to bed. In essence, the patient is placed in the paradoxical position of having to perform the activity of not sleeping when in bed. If the individual acquiesces and genuinely tries to remain awake in bed, performance anxiety over not sleeping is alleviated and sleep becomes less difficult to initiate.

Although seldom used in isolation, generic *sleep hygiene*[7] recommendations that target lifestyle and environmental conditions conducive to sleep are often provided in conjunction with other behavioral insomnia interventions. Most commonly, these recommendations encourage regular exercise; elimination of caffeine, alcohol, and nicotine; consumption of a light snack at bedtime; and sleeping in a quiet, dark, and comfortable bedroom.

*Cognitive therapy,* an approach that alters dysfunctional cognitions contributing to sleep difficulties, has also been used to address insomnia complaints. When applied specifically to insomnia patients, cognitive therapy targets unrealistic expectations about sleep as well as misconceptions or misattributions regarding the causes of insomnia, the consequences of insomnia, the ability to control and predict sleep, and sleep-promoting behaviors.[8] The goal of this therapy is to reduce or eliminate dysfunctional beliefs and attitudes about sleep that contribute to sleep-related performance anxiety and sleep-disruptive habits.

Although each of the therapies discussed thus far have their merits, none can be considered an omnibus approach that addresses the range of behavioral, physiological, and psychological factors that perpetuate insomnia. As a consequence, multicomponent, *cognitive-behavioral therapy (CBT)* approaches have emerged and become increasingly popular for insomnia management. CBT combines cognitive therapy with other behavioral therapies, such as stimulus control, sleep restriction, sleep hygiene, and, occasionally, relaxation training, to address the multitude of perpetuating mechanisms currently thought to sustain chronic insomnia.[8,9] Given its relatively broad focus, CBT overcomes the limitations of the previously mentioned, first generation behavioral approaches and meets the treatment needs of a wider array of insomnia sufferers.

## Treatment Delivery and Accessibility

In practice, CBT and other behavioral insomnia treatments are typically provided in a series of individual treatment sessions. Both brief (one or two sessions) as well as more extended (six to eight sessions) individual treatment models have been described in the literature.[3] Given the expense of individualized therapy, a number of alternate treatment delivery models have been tested. Several studies have shown group CBT (4–12 individuals per group), provided in 6–8 sessions, is a viable and effective alternative to individualized treatment.[1,3,10] Telephone consultation also appears to be a viable alternative that produces results similar to group and

individualized treatment.[1,3] Other treatment delivery mediums, including self-help bibliotherapy, the internet, and television, have also been tested but appear somewhat less promising.[1]

At present, access to behavioral insomnia therapies remains less than optimal. Currently, there is a relative paucity of trained sleep specialists who can administer such treatments.[1] Furthermore, in the United States, lack of insurance coverage for these therapies may present a financial barrier to many patients. Recently described behavioral insomnia therapies that can be administered by allied health personnel (e.g. office nurses) or primary care physicians themselves may help address this problem.[1,3,10] Additionally, the American Academy of Sleep Medicine has recently instituted several measures to enhance access to these therapies, including offering an annual Behavioral Sleep Medicine Course open to M.D. and non-M.D. health care providers and commissioning a behavioral sleep medicine committee to study methods for enhancing insurance reimbursement for behavioral insomnia treatments. Hopefully, efforts such as these will provide improved access to the available behavioral insomnia treatments.

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# Efficacy of Behavioral and Psychological Treatments of Chronic Insomnia

## Charles Morin, Ph.D.

Behavioral and psychological interventions that have received adequate validation for the treatment of chronic insomnia include sleep restriction, stimulus control therapy, relaxation, cognitive therapy, sleep hygiene education, and a combination of those methods, usually referred to as cognitive-behavior therapy.[1] The primary objective of these interventions is to remove those factors that perpetuate or exacerbate sleep difficulties over time. Such features may include hyperarousal, poor sleep habits, irregular sleep-wake schedules, and misconceptions and excessive worry about sleep and insomnia.

### Evidence for Efficacy

Treatment outcomes from controlled studies of behavioral and psychological interventions have been summarized in three meta-analyses.[2–4] Evidence from these quantitative reviews show that treatment produces reliable changes on several sleep parameters (see Table 1), including sleep latency (effect sizes ranging from 0.87 to 1.05), number of awakenings (0.53–0.83), duration of awakenings (0.65–1.03), total sleep time (0.42–0.49), and sleep quality ratings (0.94–1.44). The magnitude of those therapeutic effects is considered large ($d > 0.8$) for sleep latency and sleep quality and moderate ($d > 0.5$) for other sleep parameters. When converted into percentile ranks, these data indicate that between 70 and 80 percent of patients with insomnia benefit from behavioral and psychological treatment. Only a small proportion (20–30 percent) achieves full remission (i.e., symptom-free) after treatment, but the majority obtains significant (greater than 50 percent) symptom reduction on measures of sleep latency and time awake after sleep onset, with absolute values of those parameters falling below or near the 30-minute criterion used to define sleep onset and maintenance insomnia.[1–4] Total sleep time is increased by about 30 minutes, from 6 to 6.5 hours, and sleep quality is enhanced as well. Findings from meta-analyses represent conservative estimates of treatment effects as they are based on averages computed across all behavioral interventions and insomnia diagnoses (i.e., primary and secondary). Comparisons of single treatment modalities suggest a slight advantage for stimulus control and sleep restriction therapies. There is a trend currently, however, for most investigators to combine cognitive-behavioral approaches, which may produce broader and more clinically significant impact on daytime functioning parameters.

Treatment outcome has been documented primarily with prospective daily sleep diaries, with approximately 25 percent of randomized clinical trials using polysomnography[5–7] and another 20 percent using wrist-actigraphy.[8] Although the magnitude of improvements is usually smaller on the later measures, it does parallel clinical changes reported by patients on daily sleep diaries. Collectively, these findings indicate that treatment does not only alter patients' sleep perception but also produces physiological changes on sleep continuity measures.

**Table 1.** Mean Effect Sizes of Psychological and Behavioral Treatments for Insomnia

| Authors/Variables | SOL | NA | WASO | TST | SQ |
|---|---|---|---|---|---|
| Morin et al. (1994) | 0.88 (0.67) [a] | 0.53 (0.67) | 0.65 (0.67) | 0.42 (0.64) | n/a |
| Murtagh and Greenwood (1995) | 0.87 (0.58–1.16) [b] | 0.63 (0.63–0.63) | n/a | 0.49 (0.49–0.49) | 0.94 (0.28–1.60) |
| Smith et al. (2002) | 1.05 (0.76) [a] | 0.83 (1.30) | 1.03 (0.19) | 0.46 (0.62) | 1.44 (1.20) |

[a] Standard deviations; [b] 95 percent confidence intervals.

Note: SOL = sleep-onset latency; NA = number of awakenings; WASO = wake after sleep onset; TST = total sleep time; SQ = sleep quality; n/a = not available.

## Evidence for Generalizability

Most treatment studies, until recently, had focused on primary insomnia in otherwise healthy, young, and medication-free patients. Evidence from several recent studies suggests that patients with medical and psychiatric conditions can also benefit from insomnia-specific treatment, even though the outcome with those patients is more modest than in primary insomnia. Controlled studies have documented the benefits of cognitive-behavior therapy for treating insomnia associated with chronic pain,[9] cancer,[10] and various medical conditions in older adults.[11] The findings from secondary insomnia studies indicate that baseline and posttreatment insomnia symptom measures are usually more severe among patients with comorbid disorders, but the absolute changes on those outcomes during treatment are comparable to patients with primary insomnia.

Some early studies suggested that older adults did not respond to treatment as well as younger adults, but more recent findings indicate that they can benefit from treatment, particularly when screened for other sleep disorders (e.g., sleep apnea).[6,7,11] There is also evidence that a supervised withdrawal program, with or without cognitive-behavior therapy, can facilitate discontinuation of hypnotic medications among prolonged users.[12,13]

## Long-Term Outcomes

A reliable finding across studies with follow-ups is that behavioral treatment produces stable changes in sleep patterns over time. Indeed, several studies with long-term follow-up data have shown that sleep improvements observed at posttreatment are well maintained up to 6, 12, and 24 months after treatment completion.[5–8] Long-term outcomes must be interpreted cautiously, however, as few studies report long-term data and, among those that do, attrition rates increase over time. In addition, a substantial proportion of patients who benefit from short-term therapy remain vulnerable to recurrent episodes of insomnia in the long-term. There is a need to evaluate the effects of long-term maintenance therapies to prevent or minimize the frequency and severity of those episodes.

## Needs for Future Research

Despite recent progress made in the treatment of insomnia, there are several unresolved issues in need of further research. For instance, there is little information about the impact of insomnia treatment on measures of daytime functioning, quality of life, and psychological well-being. Also, while there is evidence supporting the *efficacy* of behavioral and psychological treatment, there is still little information about its clinical *effectiveness*[8] when implemented in clinical practices. Another challenge for the future will be to optimize outcome. Although most treated individuals are considered treatment responders, only a minority achieve full remission, and a substantial proportion continue to experience residual sleep difficulties and remain at risk for insomnia. Ongoing studies are examining what the optimal dosage of therapy is and whether the addition of maintenance and individualized therapy would enhance outcome. Additional studies are also needed to evaluate whether the addition of sleep medication to behavioral intervention has an additive or subtractive effect on short- and long-term outcomes. On the practical side, an important challenge will be to disseminate more efficiently validated behavioral interventions. Innovative treatment implementation models using nurse practitioners,[8] telephone consultations,[14] self-help materials, and the Internet could facilitate access to treatment.

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# Efficacy of Benzodiazepine Receptor Agonists in the Treatment of Chronic Insomnia

**James K. Walsh, Ph.D.**

Eight benzodiazepine receptor agonists (BzRAs) are currently approved for the treatment of insomnia by the U.S. Food and Drug Administration. The term BzRA is derived from the recognized site of action of these drugs, which involves occupation of benzodiazepine receptors on the gamma-aminobutyric acid, type A (GABAA) receptor complex and facilitation of gamma-aminobutyric acid inhibition.

The appropriate medical use of hypnotics for insomnia is currently controversial. The National Institutes of Health guidelines from 1983[1] have been labeled as no longer current for medical practice. The majority of authors recommend BzRAs for short-term use, either for acute or chronic forms of insomnia. Some experts advocate nightly, long-term use of BzRAs in certain situations; others recommend intermittent use of BzRAs for chronic insomniacs.

Hypnotic efficacy variables have predominantly been measures of sleep induction, maintenance, and quality. Sleep induction and maintenance are measured with polysomnographic (PSG) recordings and/or patient reports. Sleep latency (whether PSG or self-report) is the standard sleep induction variable, and the number of awakenings and wake after sleep onset are the most common sleep maintenance measures. Total sleep time and sleep efficiency reflect both sleep induction and sleep maintenance properties. Sleep quality does not have an established PSG metric, but a variety of patient-reported or investigator-rated measures relate to the sleep quality construct.

Many studies have documented the hypnotic efficacy of BzRAs using patient reports, PSG, or both. Meta-analyses found medium to large effect sizes when comparing BzRAs to placebo on the following efficacy measures for chronic insomniacs: total sleep time (0.71–0.84), sleep latency (0.45–0.56), wake after sleep onset (0.89), number of awakenings (0.65–0.97), and sleep quality (0.62–1.20).[2,3] However, these meta-analyses have limitations because they combine data from multiple drugs at multiple doses with widely different pharmacokinetics, all of which may impact the outcome variables examined in the meta-analyses.

At the currently recommended doses, all of the BzRA hypnotics reduce sleep latency and most increase total sleep time. An exception is zaleplon, which does not reliably increase total sleep time. Specific sleep maintenance variables, as distinct from total sleep time, have not been commonly reported efficacy variables until recently.

A large number of studies document that the efficacy of BzRAs is present on the first night of administration in both acute and chronic insomnia. A large majority of hypnotic studies have been conducted with primary insomnia, but the available evidence suggests that they show similar effects in secondary insomnias.[4,5] No studies of ethnic, racial, or gender differences have been published.

Despite what is often stated, tolerance to the hypnotic effects of BzRAs does not develop in most well-designed studies. In rigorous polysomnographic studies, zolpidem (10 mg) and

zaleplon (10 mg) have been shown to retain efficacy for 5 weeks of nightly use.[6,7] Unpublished investigations of estazolam (2 mg) and triazolam (0.25 mg) found sustained efficacy for 10–12 weeks of nightly use. A recent landmark study[8] of several hundred primary insomniacs found continued hypnotic efficacy of eszopiclone (3 mg) for 6 months of nightly use based on weekly self-reports of sleep latency, total sleep time, number of awakenings, sleep quality, and wake time after sleep onset. Nonblinded treatment with eszopiclone was continued for an additional 6 months without evidence of tolerance. Other recent studies also suggest that BzRAs maintain efficacy for treatment of insomnia for several months or more of nightly use.[9] Non-nightly use of zolpidem (10 mg) has been investigated for up to 12 weeks.[10] Ratings of sleep latency, total sleep time, number of awakenings, and sleep quality were all improved on nights with zolpidem. Additionally, investigator global ratings, which considered both medication nights and nonmedication nights, indicated reduced insomnia severity with zolpidem.

Controlled hypnotic effectiveness trials, per se, have not been carried out. However, some reports provide information which may approximate that of investigations of effectiveness. An epidemiologic study[11] found that of 532 patients chronically using hypnotics, 67 percent rated their sleep quality as improved "a lot" and only 14.4 percent reported little or no improvement. An interview study of individuals who had taken a medication to help them sleep in the past year found very high satisfaction rates.[12] Specifically, 84 percent of those taking triazolam, 82 percent taking flurazepam, 74 percent taking temazepam, and 61 percent taking over-the-counter aids reported they would take the medication for the same purpose in the future. Long-term, open-label studies also provide some information about effectiveness.[13,14] Zolpidem and zaleplon have been evaluated over periods of 6–12 months. In general, patients and physicians report sustained benefits of the hypnotics for the duration of the studies, without adverse reactions unique to long-term use.

Most definitions of insomnia include some form of subjective daytime impairment consequent to the sleep disruption. Yet, very few studies have investigated change in the daytime impairment of insomnia patients. In the 6-month eszopiclone study of primary insomniacs, patient reports of daytime alertness, ability to function during the daytime, and physical sense of well-being were all significantly improved with treatment. The waking impact of other forms of chronic insomnia may differ from primary insomnia and may respond to treatment. For example, periodic limb movement disorder[15] and rheumatoid arthritis[16] patients with insomnia have been shown to have lower than optimal Multiple Sleep Latency Test scores, which improve significantly after 6 nights of treatment with triazolam.

Future research should focus on the effects of hypnotics on sleep in: (1) insomnia with comorbid illness as well as the status of the comorbid condition (independent from sleep); (2) specific populations (i.e., older adults, ethnic and racial groups, etc.); and (3) dimensions of waking life (e.g., quality of life, cognition, occupational performance, health care utilization).

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# Benzodiazepine Receptor Agonist Safety

## Timothy Roehrs, Ph.D.

The major side effects associated with benzodiazepine receptor agonist (BzRA) use include psychomotor and cognitive (e.g., anterograde amnesia) impairment, discontinuation effects, and dependence liability.[1] Some of these side effects are mediated by the primary pharmacodynamic activity, sedation, of BzRAs and directly relate to the pharmacokinetic properties of specific BzRAs. Other side effects can be attributed to both the pharmacokinetics and receptor selectivity of the drug, and finally, drug dose and duration of use may determine other side effects as well.

Psychomotor impairment has been demonstrated on laboratory performance tests and actual roadway driving assessments with the impairment evident as slowed reaction times, response errors, and driving deviations. At peak plasma concentrations, the degree of impairment relates directly to dose. The duration of the impairment relates to both the half-life and dose of the specific BzRA. When the impairment extends to the morning following nighttime administration, it has been referred to as "residual effects" (i.e., a prolongation of the sedative effect of the drug). Studies using performance and driving assessments and the Multiple Sleep Latency Test have shown differences in residual effects between short- and long-acting drugs and between doses of the same drug.

Cognitive impairment, most typically anterograde amnesia, is another major side effect of BzRAs. Anterograde amnesia is memory failure for information presented after consumption of the drug. It is, in part, related to the sedative effects of the BzRAs and is determined by the pharmacokinetics of the drug. The level of plasma concentration and, hence, the degree of sedation at the time of information input will determine the degree of amnesia (i.e. memory consolidation failure). However, amnesia is also associated with the receptor selectivity of the BzRAs. BzRAs act as allosteric modulators of gamma-aminobutyric acid, type A receptors and gene knockin studies have identified and characterized various gamma-aminobutyric acid, type A receptor subunits for their pharmacological profiles. The alpha 1 receptor subtype mediates both the sleep and amnestic effects of the BzRAs.

The most frequently observed discontinuation effect of the BzRAs in clinical use is rebound insomnia.[2] Sleep is worsened for 1–2 nights relative to baseline, even after 1–2 nights of previous BzRA use, and rebound insomnia does not appear to increase in severity with the duration of night use, at least in the short-term. Rebound insomnia can occur after high doses (i.e. beyond clinical doses) of all short- and intermediate-acting BzRAs. It is unlikely to occur with long-acting drugs, due to the gradual decline in plasma concentrations inherent to their pharmacology. Rebound insomnia is an exacerbation of the original symptom (i.e. insomnia) and not a withdrawal syndrome (i.e. expression of new symptoms). The extent to which duration of administration and dose might combine to increase the likelihood of rebound is unknown.

With long-term use there is concern of dependence, as there are reports of physical and behavioral dependence with long-term daytime anxiolytic use of therapeutic doses of BzRAs.[3] However, any systematic information regarding the dependence liability of long-term therapeutic use of hypnotic doses of BzRAs is very limited. Recently, a placebo-controlled, double-blind

study of a BzRA hypnotic reported no evidence of physical and behavioral dependence after 6 months of nightly use.[4] Short-term studies of the behavioral dependence liability of BzRA hypnotics suggest they have a low behavioral dependence liability.[3] Hypnotic self-administration by insomniacs is not associated with dose-escalation, does not increase with rebound insomnia, does not generalize to daytime use, and varies as a function of the nature and severity of the patients' sleep disturbance, leading to the conclusion that the patients' hypnotic self-administration is therapy-seeking behavior.

The majority of the information regarding BzRA safety has been obtained through short-term, laboratory-based studies. A few older population-based, retrospective studies have reported increased falls in the elderly and an increased mortality associated with drugs to promote sleep. However, this increased mortality is associated with off-label use of drugs as sleep agents rather than hypnotics. One 1990 population-based study of hypnotic use reported that the majority of people used hypnotics for 2 weeks or less and the small percentage that used them on a chronic basis showed no dose escalation.[5] New nonbenzodiazepine BzRA hypnotics with improved safety profiles have been introduced since these data were collected. Thus, there is a need for new population-based information about the types and patterns of hypnotic use and the safety of BzRAs relative to other drugs used as hypnotics.

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# Systematic Review of the Efficacy and Safety of Drug Treatments and Combination Treatments in the Management of Chronic Insomnia in Adults

**Manisha Witmans, M.D., FRCPC, Dip. ABSM, F.A.A.P.**

Management of acute insomnia has traditionally involved pharmacotherapy, hypnotic medications, and complementary and alternative therapy. The use of medications is common practice for both acute and chronic insomnia, despite the fact that the U.S. Food and Drug Administration has approved none of them for long-term use for chronic insomnia. According to a Sleep in America Poll, an estimated 0.5 percent of the population takes sedative medications for insomnia for more than 1 year. In addition, more than 1 in 10 people (11 percent) report using prescription (6 percent) and/or over-the-counter medications (6 percent) at least a few nights a month to help them sleep.[1] Medications commonly used to treat insomnia include antidepressants, antihistamines, anticholinergics, benzodiazepines, and nonbenzodiazepine hypnotics. Many questions and challenges related to medication use for chronic insomnia remain, such as the appropriate treatment for different types of primary and secondary insomnia and the long-term side effects and daytime consequences of using such agents.

The Evidence-based Practice Center's objective was to conduct a systematic review of the efficacy and safety of drug treatments and combination treatments in the management of chronic insomnia in adults. A systematic search of 21 electronic databases was conducted. The following databases were searched: MEDLINE®, EMBASE, CINAHL®, Ovid MEDLINE® in-process and other nonindexed citations, Ovid OLDMEDLINE®, PsycINFO®, EBM Reviews–Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts, AMED (Allied and Complementary Medicine Database), HealthSTAR/Ovid HealthSTAR, EBM Reviews–Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Science Citation Index Expanded™, Biological Abstracts, Cochrane Complementary Medicine Field Registry, CAB Abstracts, SIGLE, OCLC Proceedings First, Dissertation Abstracts, Alt HealthWatch, NLM Gateway, and PubMed®.

A study was considered to be relevant to the review if it involved a drug intervention or combined drug and psychological intervention and met the following criteria: (1) the report was written in English; (2) the majority of participants were at least 18 years old; (3) participants suffered from chronic insomnia defined as a sleep disturbance of at least 1 month in duration; (4) participants were randomized to intervention or placebo, except for studies involving a combined drug and psychological intervention in which case a placebo group was not required; (5) participants and assessors were blind to treatment received, except for studies involving combined drug and psychological interventions; and (6) it assessed at least one of the following outcomes: sleep onset latency (SOL), wakefulness after sleep onset, sleep efficiency, total sleep time, sleep quality, or quality of life. SOL was the primary outcome.

If the majority of participants met one of the following criteria, the study population was considered to suffer from chronic insomnia: (1) participants suffered from a sleep disturbance of 4 weeks or more; (2) participants were described as having a chronic sleep disturbance; or (3) participants were selected from a sleep disorders clinic. The Jadad Scale was used to assess

study quality. The concealment of treatment allocation was also assessed. Data were analyzed quantitatively using the Random Effects Model.

SOL was significantly decreased by benzodiazepines (mean difference [MD]: -16.5; 95 percent confidence interval [CI]: [-20.5, -12.5]), nonbenzodiazepines (MD: -18.1; 95 percent CI: [-22.5, -13.7]), and antidepressants (MD: -7.4; 95 percent CI: [-10.5, -4.4]). Wakefulness after sleep onset was significantly decreased by benzodiazepines (MD: -23.1; 95 percent CI: [-35.7, -10.5]), nonbenzodiazepines (MD: -12.6; 95 percent CI: [-23.0, -2.3]), and antidepressants (MD: -11.4, 95 percent CI: [-16.2, -6.6]). All of the preceding interventions had a significantly higher risk of harm compared to placebo: benzodiazepines (risk difference [RD]: 0.15; 95 percent CI: [0.10, 0.20]), nonbenzodiazepines (RD: 0.05; 95 percent CI: [0.01, 0.09]), and antidepressants (RD: 0.09; 95 percent CI: [0.01, 0.18]). Only eight studies were identified that analyzed the efficacy of combined treatments for chronic insomnia. A number of comparisons emerged between combined drug and psychological treatments and either single treatment or placebo. Each of these comparisons encompassed a small number of studies and many of them could not be pooled because of important differences in interventions. The results of meta-analyses for individual comparisons and a qualitative description of the studies will be provided.

There is evidence that benzodiazepines and nonbenzodiazepines are effective treatments in the management of chronic insomnia. There is some evidence that antidepressants are effective in the management of chronic insomnia; however, more research is required in this area. There is evidence that benzodiazepines, nonbenzodiazepines, and antidepressants pose a risk of harm and that benzodiazepines have a higher risk of harm than nonbenzodiazepines. Additional studies are needed to determine the efficacy of combined treatments for chronic insomnia.

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# Systematic Review of the Efficacy and Safety of Nondrug and Sequential Treatments in the Management of Chronic Insomnia in Adults

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The role of psychological factors in insomnia has resulted in the development of alternative, nonpharmacological interventions for the management of insomnia. Cognitive/behavioral therapy has been recognized as a valid and successful treatment approach for insomnia.[1] Components of treatment may include sleep restriction, sleep hygiene, stimulus control, and cognitive restructuring. Various forms of relaxation therapy are used to alleviate somatized tension and cognitive arousal and may be used for management of insomnia. Many of these commonly used clinical tools have not undergone rigorous testing to determine their efficacy and long-term safety. The efficacy of these treatments has been evaluated in some studies,[1–3] but differences in the definition of insomnia and outcome measures makes it difficult to compare study results. Although complementary and alternative substances have been increasingly used in the management of insomnia, their efficacy remains unclear. Similarly, the efficacy of sequential treatments in the management of chronic insomnia is unclear.

The Evidence-based Practice Center's objective was to conduct a systematic review of the efficacy and safety of psychological and sequential treatments in the management of chronic insomnia in adults. A systematic search of 21 electronic databases was conducted. The following databases were searched: MEDLINE®, EMBASE, CINAHL®, Ovid MEDLINE® in-process and other nonindexed citations, Ovid OLDMEDLINE®, PsycINFO®, EBM Reviews–Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts, AMED (Allied and Complementary Medicine Database), HealthSTAR/Ovid HealthSTAR, EBM Reviews–Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Science Citation Index Expanded™, Biological Abstracts, Cochrane Complementary Medicine Field Registry, CAB Abstracts, SIGLE, OCLC Proceedings First, Dissertation Abstracts, Alt HealthWatch, NLM Gateway, and PubMed®.

A study was considered to be relevant to the review if it involved a psychological intervention (relaxation and cognitive/behavioral therapy) and met the following criteria: (1) the report was written in English; (2) the majority of participants were at least 18 years old; (3) participants suffered from chronic insomnia defined as a sleep disturbance of at least 1 month in duration; (4) participants were randomized to intervention or placebo; and (5) it assessed at least one of the following outcomes: sleep onset latency (SOL), wakefulness after sleep onset (WASO), sleep efficiency, total sleep time, sleep quality, or quality of life. Sleep onset latency was the primary outcome. The placebo treatment for relaxation therapy and cognitive/behavioral therapy was minimal treatment, such as sleep hygiene recommendations or minimal instruction. For sequential treatment involving combination therapy, the study was not required to have a placebo arm for inclusion in the review.

If the majority of participants met one of the following criteria, the study population was considered to suffer from chronic insomnia: (1) participants suffered from a sleep disturbance of 4 weeks or more; (2) participants were described as having a chronic sleep disturbance; or

(3) participants were selected from a sleep disorders clinic. The Jadad Scale was used to assess study quality. The concealment of treatment allocation was also assessed. Data were analyzed quantitatively using the Random Effects Model.

The nondrug interventions were classified as complementary and alternative care, relaxation therapy, and cognitive/behavioral therapy. The complementary and alternative substances reviewed included L-tryptophan, melatonin, and valerian. SOL was significantly decreased by melatonin (mean difference [MD]: -8.3; 95 percent confidence interval [CI]: [-14.5, -2.0]). SOL was not significantly reduced by either L-tryptophan (MD: -11.0; 95 percent CI: [-33.0, 11.1]) or valerian (MD: -1.3; 95 percent CI: [-21.4, 18.9]), compared to placebo; however, there were only two and three studies in each category, respectively. Melatonin did not have a significantly higher risk of harm compared to placebo (risk difference: 0.09; 95 percent CI: [-0.11, 0.29]). WASO was not significantly reduced by melatonin (MD: -9.7; 95 percent CI: [-33.6, 14.3]). There were no studies for L-tryptophan and only one study for valerian that provided data on this outcome, precluding a meta-analysis for these substances. SOL was significantly decreased by relaxation therapy with short-term treatment (less than 4 weeks) (MD: -22.0; 95 percent CI: [-41.0, -2.9]); however, WASO was not significantly reduced by relaxation therapy (MD: -1.6; 95 percent CI: [-14.1, 10.8]). WASO was significantly decreased by cognitive/behavioral therapy (MD: -18.2; 95 percent CI: [-30.4, -6.0]); however, SOL was not significantly reduced by cognitive/behavioral therapy (MD: -4.6; 95 percent CI: [-9.8, 0.6]). Only one study was identified that analyzed the efficacy of combined versus sequential treatment. The study examined the efficacy of a nonbenzodiazepine and cognitive/behavioral therapy administered in combination versus these interventions administered sequentially. The combined treatment did not significantly increase sleep efficiency (MD: 4.0; 95 percent CI: [-23.4, 31.4]) or total sleep time (MD: -25.8; 95 percent CI: [-169.9, 118.3]) compared to the sequential treatment.

There is some evidence that melatonin is effective in the management of chronic insomnia in subsets of the chronic insomnia population, and there is no evidence that melatonin poses a risk of harm. However, more research is required in this area, given that the results are based on a small number of studies. There is evidence that relaxation and cognitive/behavioral therapy are effective in the management of chronic insomnia in subsets of the chronic insomnia population. Additional studies are needed to determine the efficacy of sequential treatments in the management of chronic insomnia.

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# Use of Over-the-Counter Medicine, Complementary and Alternative Medicine, and Alcohol in the Treatment of Chronic Insomnia

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## Over-the-Counter Medicine

Americans spend billions of dollars each year on over-the-counter (OTC) medications, health foods, and dietary supplements,[1] yet there is little evidence on the efficacy of these substances. The assumption that OTC and nutritional supplements are safe just because they are not controlled is false. There are few rigorous scientific studies which support any beneficial effect of these unregulated compounds for the treatment of insomnia. Studies that have been done have used small samples, and at times, inadequate design, no statistical analysis, and few objective outcome measures.[2]

### *OTC: $H_1$-Receptor Antagonists*

Histamine is a neurotransmitter with wake-promoting properties, and in animal models, suppression of histamine has led to sedation. Of the current U.S. Food and Drug Administration (FDA)-approved OTC sleeping aids, the most frequent active ingredients are diphenhydramine hydrochloride, diphenhydramine citrate, and doxylamine succinate. Since 1987, sales have steadily increased. Most recently, these antihistamines have been combined with analgesics ("nighttime analgesics") with estimates that these medications are sold at twice the rate of the nonanalgesic sleeping aids.[3]

There are eight studies, with inconclusive results, concerning patients with sleep problems that examined efficacy of the H1-receptor antagonists that are still on the market. All were observational, patient self-report, or physician evaluation with no objective sleep measures.[2] Few were random, double-blind studies, and most had small sample sizes. While the reports on efficacy are inconclusive, there are reports that tolerability to the sedating effects of $H_1$-receptor antagonists develops quickly.[4]

There are a variety of side effects reported, including sedation, diminished alertness, vomiting, depression, malaise, drowsiness, dry mouth, grogginess, weakness, headaches, gastrointestinal distress, impotence, and voiding difficulties.[2] They are contraindicated in patients with narrow angle glaucoma as these medications may increase intraocular pressure. In a study of hospitalized elderly, there was a 70 percent increased risk for impaired cognition, which was dose-related with the use of diphenhydramine for sleep.[5]

### *OTC: Herbal and Nutritional Supplements*

There are many herbal and nutritional substances sold for the treatment of insomnia, but there are almost no studies to support their efficacy or safety. The two most common are melatonin and valerian root.

#### Melatonin

The FDA does not regulate melatonin, therefore formulations of it are not standardized and different preparations have been used in clinical trials. The few studies that compared effects of melatonin to other pharmacological agents in the treatment of sleep disorders found that melatonin was not as effective as either zopiclone or zolpidem. A major review of melatonin recently conducted by the Agency for Healthcare Research and Quality by the University of Alberta Evidence-based Practice Center concluded that, in general, studies have been of questionable quality.[6] The magnitude of the effects of melatonin appears to be of no clinical significance in insomnia. Short-term use of melatonin appears to be safe, but there are little data on its long-term use.

#### Valerian Root

Valerian *(Valeriana officinalis)* root is an herb that is widely used to promote sleep with its sedative properties attributed to a benzodiazepine-like activity. Sales of valerian preparations totaled $8 million in the United States between 1997 and 1998.[7] Over the past two decades, a number of controlled clinical trials have investigated the effects of valerian on sleep but mostly in normal subjects with inconsistent results. There is only one study of valerian in patients with insomnia. A single dose had no significant effect on sleep. A 14-day course was associated with shorter sleep latency and shorter latency to deep sleep by sleep recording, but there were no significant differences in subjective sleep quality or other objective sleep parameters. Adverse effects of valerian are rare and have been reported to be mild in general, including lightheadedness, headache, and "hangover." However, there have been case reports of hepatotoxicity in individuals taking herbal products containing valerian and one report of heart failure and delirium following sudden withdrawal of valerian.[2]

#### Other Herbal Products for Insomnia

There are many other herbal products that are sold for insomnia (e.g., passionflower, Jamaican dogwood, hops, chamomile, lemon balm, St. John's Wort, skullcap, California poppy, lavender), but there have been no studies of efficacy or safety.[2] The FDA issued an advisory statement for consumers regarding the potential risk for hepatotoxicity with kava kava.

## Complementary and Alternative Medicine Treatments

### *Light*

Light treatment is recommended for depression and circadian rhythm disorders. Studies of insomnia have primarily been in older populations with and without dementia and include

mixed results. Minor side effects have been noted, including eye irritation, headache, nausea, and dryness of eyes. Hypomania in patients with bipolar affective disorders is rare.[8]

### *Exercise*

A meta-analysis of the extant literature concluded that acute exercise had virtually no effect on sleep latency or wake time, a modest but statistically significant increase in total sleep time and deep sleep, and a significant increase in rapid eye movement latency and decrease in rapid eye movement sleep amount.[9] In general, studies of the effect of chronic exercise on sleep have not yielded compelling evidence that exercise promotes sleep. Much of this literature, however, has been limited to good sleepers.

### *Passive Body Heating*

There have been a handful of studies showing that passive body heating (i.e., taking a hot bath for 30 minutes before bedtime) delays core body temperature and improves sleep efficiency in older patients with insomnia.[10]

### *Acupuncture*

In traditional Chinese medicine, acupuncture is used for the treatment of insomnia. One polysomnogram (sleep recording) study conducted before and after treatment showed a statistically significant effect on sleep in patients who received acupuncture versus placebo.[11]

### *Low Energy Emission Therapy (LEET)*

LEET delivers low levels of amplitude-modulated, radio frequency, electromagnetic fields. There have been very few studies on the efficacy and safety of LEET in patients with insomnia. The largest study in patients with chronic insomnia evaluated efficacy and found improvement in sleep with no rebound insomnia and no significant side effects.[12]

## Alcohol

About 30 percent of patients with chronic insomnia use alcohol to induce sleep,[13] but few studies have examined the effect on sleep in insomniacs. Roehrs et al.[14] found that 0.5 g/kg of alcohol improved sleep in patients with insomnia but not in age-matched normal controls.

In conclusion, most evidence does not support the use of OTC or herbal preparations. More research is needed on the efficacy and, in some cases, on safety of OTC medications, complementary and alternative medicine, and alcohol in patients with insomnia. Specifically, randomized, placebo-controlled, objective sleep studies in patients with insomnia are needed, as are studies comparing the efficacy and safety of these substances to commonly prescribed hypnotics.

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# Use of Off-Label Medications in the Treatment of Chronic Insomnia

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The pharmacologic approach to the treatment of insomnia in the United States took a quizzical turn in the 1990s. The overall rate at which prescribed medications were used for the treatment of insomnia fell in outpatient practice by 24 percent between 1987 and 1996. Furthermore, the absolute use of U.S. Food and Drug Administration (FDA)-approved hypnotics declined in the treatment of insomnia by 54 percent, while the use of trazodone and other sedating antidepressants rose by 146 percent.[1] This trend continued through 2002, such that trazodone became the most frequently used medication for the treatment of insomnia[2] and the first-line choice among psychiatrists treating serotonin reuptake inhibitor (SSRI)-related insomnia, preferred by 78 percent.[3] In addition to trazodone, a wide variety of antidepressants, antipsychotics, and sedatives gained favor for the treatment of insomnia, despite the fact that none of these medications are approved for the treatment of insomnia.[2]

The preferential use of unapproved medications for the treatment of insomnia suggests that there must be substantial evidence supporting this practice. A review of the literature was conducted, searching PubMed with the term insomnia crossed against the 10 unapproved prescription medications most commonly used for insomnia—trazodone, amitriptyline, mirtazapine, quetiapine, clonazepam, hydroxyzine, alprazolam, lorazepam, olanzapine, and doxepin. The review was not intended to be exhaustive but instead focused on quality placebo randomized controlled trials (RCT) of these agents in chronic insomnia. When no trials were available in chronic insomnia, transient insomnia was considered. When no RCTs were available, well-done trials without placebo were considered. Studies describing medication effects in either primary or secondary insomnia were included, and information regarding residual effects the following morning and effects on sleep architecture were noted.

Trazodone (100 mg) has been studied in a 2-week comparative RCT against placebo and zolpidem in a sample of 278 primary insomniacs. Outcome was derived from patient-report.[4] Trazodone and zolpidem were comparable in their action in sleep latency and total sleep time in the first week, and both were superior to placebo. However, by the end of the second week, only zolpidem was superior to placebo, while trazodone had merged with placebo. Trazodone's effect on electroencephalogram (EEG) sleep is distinguished by a selective increase in slow wave sleep (SWS), at least in normal sleepers over 2 weeks or less.[5–7] Trazodone may have utility in treating insomnia that persists during antidepressant treatment, improving self-reported sleep in a 1-week RCT of 17 patients,[8] and while reducing awakenings and increasing SWS in a RCT EEG study lasting 1 week in 7 patients.[9]

There was no information available regarding the effects of amitriptyline on sleep. There is no data on the effects of mirtazapine in chronic insomnia. There are two RCTs of mirtazapine (30 mg) in transient insomnia in otherwise good sleepers, capitalizing on the first night effect in the sleep lab. These small studies of 6 and 20 patients, respectively, were associated with better sleep induction, better sleep maintenance, and increased SWS.[10,11] However, mirtazapine appears to slow motor reaction times the day after bedtime dosing.[12]

There are no RCTs of quetiapine in chronic insomnia. However, a single RCT showed quetiapine (25–100 mg) was superior to placebo in increasing EEG total sleep time and improving subjective sleep quality in a one night transient insomnia study of 14 normal sleepers using environmental noise to disturb sleep.[13] The 100 mg dose, however, was associated with induction of periodic limb movements (PLM).

There are no RCTs of clonazepam in chronic primary insomnia. A single-armed study in 6 chronic insomniacs showed clonazepam improved sleep compared to baseline.[14] Two large RCTs of clonazepam in insomnia associated with depression in fluoxetine patients found that clonazepam (0.5–1.0 mg) at bedtime was superior to placebo in its effect on subjective sleep for the first 3 weeks of administration in 80 subjects[15] but not for longer periods in 50 patients.[16] Similarly, two studies suggested that clonazepam improves EEG sleep up to 1 month in patients with PLM disorder, although the interpretation of these studies is limited by lack of a placebo comparator in a study of 26 patients with mixed PLM and restless leg syndrome[17] and was limited by a mixing of insomnia and hypersomnia complaints in a sample of 20 PLM patients.[18]

There are no RCTs of hydroxyzine in sleep and no modern non-RCTs in sleep. There are no RCTs of alprazolam in insomnia, but there is a study of 6 primary insomniacs treated with alprazolam (1 mg) whose EEG sleep improved compared to baseline.[19]

Two RCTs of lorazepam (1.5–3.0 mg) have shown improvement in subjective and EEG sleep for up to 18 nights in 12 and 6 chronic insomniacs, respectively.[20,21] Lorazepam (1, 2, 2.5, and 4 mg) has also been shown to be superior in improving subjective sleep in a single-dose RCT in various transient insomnia models.[22–24] However, one single-arm study[21] and three RCTs[23,25,26] strongly suggest that bedtime doses of lorazepam (1–4 mg) are associated with deterioration in the digit symbol substitution test, card sorting, coordination, decreased reaction time, and greater confusion.

There are no RCTs of olanzapine in chronic insomniacs, but a single-dose RCT using the transient insomnia model in 9 good sleepers showed better subjective sleep quality, improved EEG sleep continuity, and greater SWS.[27]

A single RCT of doxepin (25–50 mg) in 47 primary insomniacs showed sustained advantages over 4 weeks in EEG total sleep time, sleep efficiency, subjective sleep quality, and next-day ability to work.[28]

Overall, the evidence suggests that both trazodone and lorazepam have short-term benefits for both chronic and transient insomnia. Clonazepam has evidence of benefit for 3–4 weeks in insomnia secondary to depression or PLMs. Doxepin has evidence of benefit in primary insomnia for 4 weeks. Trazodone, mirtazapine, and olanzapine acutely increase SWS—theoretically, a potential benefit not seen in approved hypnotics. There is no placebo RCT showing evidence of hypnotic efficacy for alprazolam, amitriptyline, mirtazapine, quetiapine, or olanzapine. Residual effects were rarely considered with any of these medications, but residual effects were found when sought.

Given the paucity of data to support the use of off-label prescribed medications in the treatment of insomnia, why are they used so often? There is no data on this matter, but speculative possibilities include: (1) provider concerns about using FDA-approved, controlled substances for sleep for longer than their indicated duration of use in the package label;

(2) erroneous beliefs on the part of providers that off-label medications are proven to be as efficacious and perhaps safer than approved hypnotics; and (3) cost and managed care formulary considerations.

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